PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 39/395, C12Q 1/68, G01N 33/53, C12P 21/04, C12N 15/63, 15/85, 15/11, C07H 21/04

A1

(11) International Publication Number: WO 99/62547

(43) International Publication Date: 9 December 1999 (09.12.99)

(21) International Application Number: PCT/US98/11348

(22) International Filing Date: 3 June 1998 (03.06.98)

(71) Applicant *(for all designated States except US)*: THE REGENTS OF THE UNIVERSITY OF CALIFORNIA [US/US]; 12th floor, 1111 Franklin Street, Oakland, CA 94607-5200 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ROME, Leonard, H. [US/US]; 18141 Rancho Street, Tarzana, CA 91356 (US). KICKHOEFER, Valerie, A. [US/US]; 3918 Scadlock Lane, Sherman Oaks, CA 92354 (US).

(74) Agents: FARAH, David, A. et al.; Sheldon & Mak, 9th floor, 225 S. Lake Avenue, Pasadena, CA 91101 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

**Published**
*With international search report.*

(54) Title: HUMAN MINOR VAULT PROTEIN p193

(57) Abstract

Purified human minor vault protein p193 or purified biologically active variants thereof, or a combination of purified human minor vault protein p193 and biologically active variants thereof are disclosed. A polynucleotide molecule encoding human minor vault protein p193, or the complementary DNA is also disclosed. Furthermore, a method of diagnosing and a method of treating patients with multidrug resistant cancer is provided.

*FOR THE PURPOSES OF INFORMATION ONLY*

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

| | |
|---|---|
| AL | Albania |
| AM | Armenia |
| AT | Austria |
| AU | Australia |
| AZ | Azerbaijan |
| BA | Bosnia and Herzegovina |
| BB | Barbados |
| BE | Belgium |
| BF | Burkina Faso |
| BG | Bulgaria |
| BJ | Benin |
| BR | Brazil |
| BY | Belarus |
| CA | Canada |
| CF | Central African Republic |
| CG | Congo |
| CH | Switzerland |
| CI | Côte d'Ivoire |
| CM | Cameroon |
| CN | China |
| CU | Cuba |
| CZ | Czech Republic |
| DE | Germany |
| DK | Denmark |
| EE | Estonia |
| ES | Spain |
| FI | Finland |
| FR | France |
| GA | Gabon |
| GB | United Kingdom |
| GE | Georgia |
| GH | Ghana |
| GN | Guinea |
| GR | Greece |
| HU | Hungary |
| IE | Ireland |
| IL | Israel |
| IS | Iceland |
| IT | Italy |
| JP | Japan |
| KE | Kenya |
| KG | Kyrgyzstan |
| KP | Democratic People's Republic of Korea |
| KR | Republic of Korea |
| KZ | Kazakstan |
| LC | Saint Lucia |
| LI | Liechtenstein |
| LK | Sri Lanka |
| LR | Liberia |
| LS | Lesotho |
| LT | Lithuania |
| LU | Luxembourg |
| LV | Latvia |
| MC | Monaco |
| MD | Republic of Moldova |
| MG | Madagascar |
| MK | The former Yugoslav Republic of Macedonia |
| ML | Mali |
| MN | Mongolia |
| MR | Mauritania |
| MW | Malawi |
| MX | Mexico |
| NE | Niger |
| NL | Netherlands |
| NO | Norway |
| NZ | New Zealand |
| PL | Poland |
| PT | Portugal |
| RO | Romania |
| RU | Russian Federation |
| SD | Sudan |
| SE | Sweden |
| SG | Singapore |
| SI | Slovenia |
| SK | Slovakia |
| SN | Senegal |
| SZ | Swaziland |
| TD | Chad |
| TG | Togo |
| TJ | Tajikistan |
| TM | Turkmenistan |
| TR | Turkey |
| TT | Trinidad and Tobago |
| UA | Ukraine |
| UG | Uganda |
| US | United States of America |
| UZ | Uzbekistan |
| VN | Viet Nam |
| YU | Yugoslavia |
| ZW | Zimbabwe |

# HUMAN MINOR VAULT PROTEIN p193

## STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

The present invention was made with government support under Grant No. GM 38097, awarded by the National Institutes of Health. The United States Government has certain rights in this invention.

## BACKGROUND

Cancer is a major cause of morbidity and mortality in the United States. Treatment of cancer generally includes chemotherapy, radiation therapy and surgery. Unfortunately, most cancers cannot be cured using chemotherapy because tumor cells tend to develop resistance to several chemotherapeutic agents over time. These cancers are referred to as "multidrug-resistant cancers" (MDR).

Overexpression of a number of proteins has been found to be associated with MDR cells lines, including P-glycoprotein (Pgp) and multidrug resistance-associated protein (MRP). These proteins appear to mediate drug resistance by acting as cytotoxic drug efflux pumps. However, many MDR cancer cell lines are known which are not associated with overexpression of either P-glycoprotein or multidrug resistance-associated protein.

More recently, a protein has been described that is overexpressed in MDR tumor cell lines which do not overexpress either P-glycoprotein or multidrug resistance-associated protein. This protein was originally named Lung Resistance-related Protein (LRP), referring to the cell line in which it was originally identified. However, once the cDNA for Lung Resistance-related Protein was isolated and the corresponding protein sequence elucidated, it was found that Lung Resistance-related Protein was human major vault protein, a previously known protein.

Vaults are large, barrel-shaped, multi-subunit, cytoplasmic, ribonucleoprotein organelles found in virtually all higher organisms and in most normal tissues. Mammalian vaults consist of three proteins having molecular weights of approximately 210, 193 and 104, and a small RNA in the relative molar ratios of 1:1:24:4 in rats. The most abundant of these, the 104 kDa protein, is termed major vault protein (MVP) and corresponds to the Lung Resistance-related Protein. The minor vault protein p193, however, has not yet been

characterized.

Therefore, there remains a need for chemotherapeutic agents that will target multidrug-resistant cancers. Further, there remains a need to characterize the minor vault protein p193.

## SUMMARY

According to one embodiment of the present invention, there is provided a protein consisting essentially of purified human minor vault protein p193 or purified biologically active variants thereof, or a combination of purified human minor vault protein p193 and biologically active variants thereof. The protein can be recombinant and can have an amino acid sequence of greater than about 50% identity of the amino acid sequence as set forth in Figure 2, SEQ ID NO:2. Further, the protein can be a protein recognized by a monoclonal antibody having affinity to any of these proteins.

According to another embodiment of the present invention, there is provided a polynucleotide molecule encoding a protein according to the present invention or its complementary strands, or a polynucleotide molecule which hybridizes to a polynucleotide sequence encoding a protein according to the present invention or its complementary strands. The molecule can be RNA or DNA, or can be another polynucleotide molecule.

According to another embodiment of the present invention, there is provided a vector containing a polynucleotide molecule according to the present invention or a prokaryotic or eukaryotic host cell stably transformed or transfected by the vector.

According to another embodiment of the present invention, there is provided a high affinity monoclonal antibody which immunoreacts with a protein according to the present invention. The antibody can have an Fc portion selected from the group consisting of the IgM class, the IgG class and the IgA class.

According to another embodiment of the present invention, there is provided a method of making a monoclonal antibody which immunoreacts with human minor vault protein p193 comprising the steps of, first, administering human minor vault protein p193 to a host in an amount sufficient to induce the production of antibodies to the human minor vault protein p193 from the antibody-producing cells. Then, the antibody-producing cells are recovered from the host. Next, cell hybrids are formed by fusing the antibody-producing cell to cells capable of substantially unlimited reproduction. Then, the hybrids are cultured.

Further, the monoclonal antibodies are collected as a product of the hybrids. The cells capable of substantially unlimited reproduction can be myeloma cells.

According to another embodiment of the present invention, there is provided a method of making a protein according to the present invention comprising the steps of, first, culturing a microorganism transformed with a polynucleotide encoding human minor vault protein p193. Then, the human minor vault protein p193 is recovered.

According to another embodiment of the present invention, there is provided a method of diagnosing a patient with a multidrug-resistant cancer comprising the steps of, first, providing a sample of tissue or fluid from the patient. Then, the level of a substance selected from the group consisting of p193 protein, p193 DNA, p193 mRNA, a substantial portion of p193 protein, a substantial portion of p193 DNA, a substantial portion of p193 mRNA and a combination of one of the foregoing in the patient sample is determined. Next, the level of the substance is compared to a known range of levels for the substance in patients with multidrug-resistant cancers. A diagnosis of multidrug-resistant cancer is made when the level of the substance determined is within the range of levels for the substance in patients with multidrug-resistant cancers. The sample can be selected from the group consisting of bone marrow, cerebral spinal fluid, blood, tears, saliva and a biopsy specimen.

According to another embodiment of the present invention, there is provided a method of treating a patient with multidrug-resistant cancer comprising the steps of, first, diagnosing a patient with multidrug-resistant cancer according to the present invention, and then treating the patient. The treatment can comprise administering to the patient antibodies having an affinity for a substance selected from the group consisting of p193 protein and a polynucleotide encoding p193. The treatment can also comprise administering to the patient at least one antisense polynucleotide having an affinity for a polynucleotide encoding p193. The treatment can further comprise administering to the patient at least one drug that blocks NAD, such as PD128763 and 3-aminobenzamide.

## FIGURES

These and other features, aspects and advantages of the present invention will become better understood with regard to the following description, appended claims, and accompanying figures where:

Figure 1 shows the complete sequence of cDNA encoding human minor vault

protein p193, top strand, and its complementary strand; and

Figure 2 shows the complete amino acid sequence of human minor vault protein p193 indicating specific regions of function.

## DESCRIPTION

The present invention involves the elucidation of the amino acid sequence for human vault protein p193, as well as the DNA sequence encoding human vault protein p193. These sequences are then utilized in methods of diagnosing multidrug resistance cancer and in methods of treating multidrug resistance cancer.

### (1) Elucidation of the Human Minor Vault Protein p193 Amino Acid Sequence and the Nucleotide Sequence Encoding Human Minor Vault Protein p193:

The human minor vault protein p193 amino acid sequence and the nucleotide sequence encoding human minor vault protein p193 were elucidated as follows. First, human vault protein p193 was cloned using an interaction trap, two-hybrid system according to techniques known to those with skill in the art. See, for example, Golemis, et al., *Current Protocols in Mol. Biol.* 20.1.1-20.35 John Willey & Sons, 1997, incorporated by reference in its entirety. In summary, rat major vault protein, GenBank accession number U09870, having the 67 amino acids at the amino-terminal truncated was used as bait against a HeLa acid fusion cDNA library obtained from Roger Brent, Boston, MA, USA to search for proteins that interacted with rat major vault protein. The interacting proteins were identified by their ability to give rise to blue colonies on media containing galactose and X-gal, a color indicator substrate. The specificity of the interaction between the identified proteins and the rat major vault protein was verified by retransformation of the identified proteins with specific, rat major vault protein and nonspecific (lexA-bicoid) bait cDNAs. This technique identified the cDNA encoding the 193 kDa minor vault protein, SEQ ID NO:1, by its interaction with the rat major vault protein.

Referring now to Figure 1, there is shown the complete sequence of cDNA encoding human minor vault protein p193, top strand, SEQ ID NO:1, and its complementary strand. As can be seen, the DNA encoding human minor vault protein p193 contains 5490 base pairs. The open reading frame is from residue 107 to residue 5281.

The cDNA encoding human minor vault protein p193 was then used to deduce the amino acid sequence of the human minor vault protein p193, SEQ ID NO:2. Further,

human minor vault protein p193 was purified from vaults by electrophoresis on 5% SDS-polyacrylamide gels. The gels were stained with copper (BioRad Laboratories, Hercules, CA, USA) and the identified band was excised and destained, and the amino acids sequenced according to standard techniques using a Finnigan TSQ-7000 Triple Quadrupole Mass Spectrometer. This sequence is the same as SEQ ID NO:2.

Referring now to Figure 2, there is shown the complete amino acid sequence of human minor vault protein p193, SEQ ID NO:2. As can be seen, the sequence includes 1724 amino acid residues.

A search of the National Center for Biotechnology databases was performed to determine if either SEQ ID NO:1 or SEQ ID NO:2 were previously known. The search revealed a previously known nucleotide sequence, GenBank accession number D79999, having 5085 nucleotides which were identical to residues 384-5469 of SEQ ID NO:1. GenBank accession number D79999 did not, however, include residues 107-383 of SEQ ID NO:1 which constitutes part of the open reading frame.

The search further revealed that residues 209-563 of SEQ ID NO:2 share 28% identity to residues 609-1004, the catalytic subunit of poly (ADP-ribose) polymerase, GenBank accession number M32721, but did not otherwise reveal a homologous sequence. This catalytic subunit binds to NAD, hydrolyzes the nicotine moiety and polymerizes the ADP ribose group.

Analysis of SEQ ID NO:2 using the PROSITE protein database also revealed that residues 1-94 of SEQ ID NO:2 comprise a BRCT domain. BRCT domains refer to the C-terminus of the cancer susceptibility gene BRCA 1, and are a superfamily of conserved domains in DNA damage-response cell cycle checkpoint proteins. See, for example, Bork, et al., The Faseb J. 11:68-76, 1997; and Callebaut, I. and Mornon, J-P., FEBS Letter 400:25-30, 1997, incorporated by reference in their entirety.

Referring again to Figure 2, residues 1-94 of human minor vault protein p193, which comprise the BRCT domain, are indicated by the unshaded box. Residues 209-563 of human minor vault protein p193, which share 28% identity to the catalytic subunit of poly (ADP-ribose) polymerase are shown in the upper shaded box. Finally, residues 1562-1724 of human minor vault protein p193, which comprise the region necessary for interaction with human major vault protein, are shown in the lower shaded box.

(2) **Generation of Antibodies to Human Minor Vault Protein p193:**

Antibodies which immunoreact with human minor vault protein p193 were produced as follows. First, fragments of human minor vault protein p193 were generated using PCR techniques. The fragments consisted of residues 408-611 and residues 1471-1724 of SEQ ID NO:2. Next, fusion proteins were generated and both polyclonal and monoclonal antibodies were produced. These antibodies recognized human minor vault protein p193 in western blots, by immunofluorescence microscopy and by immunoprecipitation.

(3) **Description of Certain Embodiments of the Present Invention:**

Therefore, according to the present invention, there is provided a protein consisting essentially of purified human minor vault protein p193, SEQ ID NO:2. The protein can also consist of purified biologically active variants of human minor vault protein p193 or a combination of purified human minor vault protein p193, SEQ ID NO:2, and biologically active variants of human minor vault protein p193. In a preferred embodiment, the protein is a recombinant protein. Further, the present invention includes a protein having an amino acid sequence of greater than about 50% identity of the amino acid sequence as set forth in SEQ ID NO:2, as well as a protein recognized by a monoclonal or polyclonal antibody having affinity to a protein according to the present invention.

The protein according to the present invention can be made according to techniques known to those with skill in the art, for example, by first culturing a microorganism transformed with a polynucleotide encoding human minor vault protein p193. Then, the human minor vault protein p193 is recovered from the microorganism.

The present invention also includes a polynucleotide molecule encoding a protein which consists essentially of human minor vault protein p193, SEQ ID NO:2, or biologically active variants of human minor vault protein p193 or a combination of purified human minor vault protein p193, SEQ ID NO:2, and biologically active variants of human minor vault protein p193, such as residues 107 to residue 5281of SEQ ID NO:1, and includes the complementary strands to these polynucleotides and a polynucleotide molecule which hybridizes to any of the foregoing polynucleotides. The polynucleotide can be an RNA molecule or a DNA molecule, as well as other polynucleotide molecules.

According to another embodiment of the present invention, there is provided a vector containing a polynucleotide according to the present invention. The vector, such as

PET 28 (available from Invitrogen, Carlsbad, CA, USA), pGEX and pSVL (both available from Amersham Pharmacia Biotech, Piscataway, NJ, USA), can be used to stably transform or transfect a prokaryotic or eukaryotic host cell.

The present invention further includes an antibody which immunoreacts with a protein or polynucleotide according to the present invention. The Fc portion of the antibody can be selected from the group consisting of the IgM class, the IgG class and the IgA class, but can also be other classes. Preferably, the antibody is a high affinity monoclonal antibody which immunoreacts with human minor vault protein p193.

The antibody can be made, for example, by administering human minor vault protein p193 to a host in an amount sufficient to induce the production of antibodies to the human minor vault protein p193 from the antibody-producing cells. Next, the antibody-producing cells are recovered from the host and cell hybrids are formed by fusing the antibody-producing cell to cells capable of substantially unlimited reproduction. Then, the hybrids are cultured and the monoclonal antibodies are collected as a product of the hybrids. Preferably, the cells capable of substantially unlimited reproduction are myeloma cells.

## EXAMPLE I

## METHOD OF DIAGNOSING A PATIENT WITH A MULTIDRUG-RESISTANT CANCER

According to one embodiment of the present invention, a patient with a multidrug-resistant cancer is diagnosed by, first, providing a sample of tissue or fluid from the patient. The sample can be bone marrow, cerebral spinal fluid, blood, tears, saliva or a biopsy specimen, or can be other suitable tissue or fluid samples. Next, the level of a substance selected from the group consisting of p193 protein, p193 DNA, p193 mRNA, a substantial portion of p193 protein, a substantial portion of p193 DNA, a substantial portion of p193 mRNA and a combination of one of the foregoing in the patient sample is determined. In a preferred embodiment, the substantial portion comprises at least about 25% of the residues of the molecule. In a particularly preferred embodiment, the substantial portion comprises at least about 50% of the residues of the molecule. Then, the level of the substance is compared to a known range of levels for the substance in patients with multidrug-resistant cancers. A diagnosis of multidrug-resistant cancer is made when the level of the substance determined is within the range of levels for the substance in patients

with multidrug-resistant cancers.

## EXAMPLE II

## METHOD OF TREATING A PATIENT WITH MULTIDRUG-RESISTANT CANCER

According to another embodiment of the present invention, a patient with a multidrug-resistant cancer is treated by disrupting the production or function of human minor vault protein p193. This is accomplished by, for example, administering to the patient antibodies having an affinity for a substance selected from the group consisting of p193 protein and a polynucleotide encoding p193. Treatment can also be accomplished by administering to the patient at least one antisense polynucleotide having an affinity for a polynucleotide encoding p193. Further, treatment can be accomplished by administering to the patient at least one drug that blocks NAD, such as PD128763 and 3-aminobenzamide.

Although the present invention has been discussed in considerable detail with reference to certain preferred embodiments, other embodiments are possible. Therefore, the spirit and scope of the appended claims should not be limited to the description of preferred embodiments contained in this application.

SEQUENCE LISTING

(1) GENERAL INFORMATION:
(i) APPLICANT: Rome, Leonard H.
Kickhoefer, Valerie A.
(ii) TITLE OF INVENTION: HUMAN MINOR VAULT PROTEIN p193
(iii) NUMBER OF SEQUENCES: 2
(iv) CORRESPONDENCE ADDRESS:
(A) ADDRESSEE: Sheldon & Mak
(B) STREET: 225 S. Lake Avenue, 9th Floor
(C) CITY: Pasadena
(D) STATE: California
(E) ZIP: 91101
(v) COMPUTER READABLE FORM:
(A) MEDIUM TYPE: Diskette, 3.50 inch, 1.44 Mb storage
(B) COMPUTER: IBM compatible
(C) OPERATING SYSTEM: Windows 95
(D) SOFTWARE: WordPerfect for Windows version 8.0
(vi) CURRENT APPLICATION DATA:
(A) APPLICATION NUMBER: to be assigned
(B) FILING DATE: filed herewith
(C) CLASSIFICATION: to be assigned
(viii) ATTORNEY/AGENT INFORMATION:
(A) NAME: Farah, David A.
(B) REGISTRATION NUMBER: 38,134
(C) REFERENCE/DOCKET NUMBER: 12401PCT
(ix) TELECOMMUNICATION INFORMATION:
(A) TELEPHONE: (626) 796-4000
(B) TELEFAX: (626) 795-6321
(2) INFORMATION FOR SEQ ID NO:1:
(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 5490 base pairs
(B) TYPE: nucleic acid
(C) STRANDEDNESS: double stranded
(D) TOPOLOGY: linear
(ii) MOLECULE TYPE: cDNA
(ix) SEQUENCE DESCRIPTION: SEQ ID NO:1:

```
CGCCCGCCCA GCCCCGGGGG CAGGGAAAGC CTAAATTACG GAATTACCGC GAGCAAGGAG      60

CGCGGAATCG GGGAGCGTCC GGAGCTAGCT GGATCCTCTA GGCAGG ATG GTG ATG        115
                                                    Met Val Met
                                                       1

GGA ATC TTT GCA AAT TGT ATC TTC TGT TTG AAA GTG AAG TAC TTA CCT        163
Gly Ile Phe Ala Asn Cys Ile Phe Cys Leu Lys Val Lys Tyr Leu Pro
     5                  10                  15

CAG CAG CAG AAG AAA AAG CTA CAA ACT GAC ATT AAG GAA AAT GGC GGA        211
Gln Gln Gln Lys Lys Lys Leu Gln Thr Asp Ile Lys Glu Asn Gly Gly
 20                  25                  30                  35
```

```
AAG TTT TCC TTT TCG TTA AAT CCT CAG TGC ACA CAT ATA ATC TTA GAT      259
Lys Phe Ser Phe Ser Leu Asn Pro Gln Cys Thr His Ile Ile Leu Asp
                40                  45                  50

AAT GCT GAT GTT CTG AGT CAG TAC CAA CTG AAT TCT ATC CAA AAG AAC      307
Asn Ala Asp Val Leu Ser Gln Tyr Gln Leu Asn Ser Ile Gln Lys Asn
            55                  60                  65

CAC GTT CAT ATT GCA AAC CCA GAT TTT ATA TGG AAA TCT ATC AGA GAA      355
His Val His Ile Ala Asn Pro Asp Phe Ile Trp Lys Ser Ile Arg Glu
        70                  75                  80

AAG AGA CTC TTG GAT GTA AAG AAT TAT GAT CCT TAT AAG CCC CTG GAC      403
Lys Arg Leu Leu Asp Val Lys Asn Tyr Asp Pro Tyr Lys Pro Leu Asp
    85                  90                  95

ATC ACA CCA CCT CCT GAT CAG AAG GCG AGC AGT TCT GAA GTG AAA ACA      451
Ile Thr Pro Pro Pro Asp Gln Lys Ala Ser Ser Ser Glu Val Lys Thr
100                 105                 110                 115

GAA GGT CTA TGC CCG GAC AGT GCC ACA GAG GAG GAA GAC ACT GTG GAA      499
Glu Gly Leu Cys Pro Asp Ser Ala Thr Glu Glu Glu Asp Thr Val Glu
                120                 125                 130

CTC ACT GAG TTT GGT ATG CAG AAT GTT GAA ATT CCT CAT CTT CCT CAA      547
Leu Thr Glu Phe Gly Met Gln Asn Val Glu Ile Phe His Leu Pro Gln
            135                 140                 145

GAT TTT GAA GTT GCA AAA TAT AAC ACC TTG GAG AAA GTG GGA ATG GAG      595
Asp Phe Glu Val Ala Lys Tyr Asn Thr Leu Glu Lys Val Gly Met Glu
        150                 155                 160

GGA GGC CAG GAA GCT GTG GTG GTG GAG CTT CAG TGT TCG CGG GAC TCC      643
Gly Gly Gln Glu Ala Val Val Val Glu Leu Gln Cys Ser Arg Asp Ser
    165                 170                 175

AGG GAC TGT CCT TTC CTG ATA TCC TCA CAC TTC CTC CTG GAT GAT GGC      691
Arg Asp Cys Pro Phe Leu Ile Ser Ser His Phe Leu Leu Asp Asp Gly
180                 185                 190                 195

ATG GAG ACT AGA AGA CAG TTT GCT ATA AAG AAA ACC TCT GAA GAT GCA      739
Met Glu Thr Arg Arg Gln Phe Ala Ile Lys Lys Thr Ser Glu Asp Ala
                200                 205                 210

AGT GAA TAC TTT GAA AAT TAC ATT GAA GAA CTG AAG AAA CAA GGA TTT      787
Ser Glu Tyr Phe Glu Asn Tyr Ile Glu Glu Leu Lys Lys Gln Gly Phe
            215                 220                 225

CTA CTA AGA GAA CAT TTC ACA CCT GAA GCA ACC CAA TTA GCA TCT GAA      835
Leu Leu Arg Glu His Phe Thr Pro Glu Ala Thr Gln Leu Ala Ser Glu
        230                 235                 240

CAA TTG CAA GCA TTG CTT TTG GAG GAA GTC ATG AAT TCA AGC ACT CTG      883
Gln Leu Gln Ala Leu Leu Leu Glu Glu Val Met Asn Ser Ser Thr Leu
    245                 250                 255
```

```
AGC CAA GAG GTG AGC GAT TTA GTA GAG ATG ATT TGG GCA GAG GCC CTG      931
Ser Gln Glu Val Ser Asp Leu Val Glu Met Ile Trp Ala Glu Ala Leu
260                 265                 270                 275

GGC CAC CTG GAA CAC ATG CTT CTC AAG CCA GTG AAC AGG ATT AGC CTC      979
Gly His Leu Glu His Met Leu Leu Lys Pro Val Asn Arg Ile Ser Leu
                280                 285                 290

AAC GAT GTG AGC AAG GCA GAG GGG ATT CTC CTT CTA GTA AAG GCA GCA     1027
Asn Asp Val Ser Lys Ala Glu Gly Ile Leu Leu Leu Val Lys Ala Ala
            295                 300                 305

CTG AAA AAT GGA GAA ACA GCA GAG CAA TTG CAA AAG ATG ATG ACA GAG     1075
Leu Lys Asn Gly Glu Thr Ala Glu Gln Leu Gln Lys Met Met Thr Glu
        310                 315                 320

TTT TAC AGA CTG ATA CCT CAC AAA GGC ACA ATG CCC AAA GAA GTG AAC     1123
Phe Tyr Arg Leu Ile Pro His Lys Gly Thr Met Pro Lys Glu Val Asn
    325                 330                 335

CTG GGA CTA TTG GCT AAG AAA GCA GAC CTC TGC CAG CTA ATA AGA GAC     1171
Leu Gly Leu Leu Ala Lys Lys Ala Asp Leu Cys Gln Leu Ile Arg Asp
340                 345                 350                 355

ATG GTT AAT GTC TGT GAA ACT AAT TTG TCC AAA CCC AAC CCA CCA TCC     1219
Met Val Asn Val Cys Glu Thr Asn Leu Ser Lys Pro Asn Pro Pro Ser
                360                 365                 370

CTG GCC AAA TAC CGA GCT TTG AGG TGC AAA ATT GAG CAT GTT GAA CAG     1267
Leu Ala Lys Tyr Arg Ala Leu Arg Cys Lys Ile Glu His Val Glu Gln
            375                 380                 385

AAT ACT GAA GAA TTT CTC AGG GTT AGA AAA GAG GTT TTG CAG AAT CAT     1315
Asn Thr Glu Glu Phe Leu Arg Val Arg Lys Glu Val Leu Gln Asn His
        390                 395                 400

CAC AGT AAG AGC CCA GTG GAT GTC TTG CAG ATA TTT AGA GTT GGC AGA     1363
His Ser Lys Ser Pro Val Asp Val Leu Gln Ile Phe Arg Val Gly Arg
    405                 410                 415

GTG AAT GAA ACC ACA GAG TTT TTG AGC AAA CTT GGT AAT GTG AGG CCC     1411
Val Asn Glu Thr Thr Glu Phe Leu Ser Lys Leu Gly Asn Val Arg Pro
420                 425                 430                 435

TTG TTG CAT GGT TCT CCT GTA CAA AAC ATC GTG GGA ATC TTG TGT CGA     1459
Leu Leu His Gly Ser Pro Val Gln Asn Ile Val Gly Ile Leu Cys Arg
                440                 445                 450

GGG TTG CTT TTA CCC AAA GTA GTG GAA GAT CGT GGT GTG CAA AGA ACA     1507
Gly Leu Leu Leu Pro Lys Val Val Glu Asp Arg Gly Val Gln Arg Thr
            455                 460                 465

GAC GTC GGA AAC CTT GGA AGT GGG ATT TAT TTC AGT GAT TCG CTC AGT     1555
Asp Val Gly Asn Leu Gly Ser Gly Ile Tyr Phe Ser Asp Ser Leu Ser
        470                 475                 480
```

```
ACA AGT ATC AAG TAC TCA CAC CCG GGA GAG ACA GAT GGC ACC AGA CTC      1603
Thr Ser Ile Lys Tyr Ser His Pro Gly Glu Thr Asp Gly Thr Arg Leu
    485                 490                 495

CTG CTC ATT TGT GAC GTA GCC CTC GGA AAG TGT ATG GAC TTA CAT GAG      1651
Leu Leu Ile Cys Asp Val Ala Leu Gly Lys Cys Met Asp Leu His Glu
500                 505                 510                 515

AAG GAC TTT CCC TTA ACT GAA GCA CCA CCA GGC TAC GAC AGT GTG CAT      1699
Lys Asp Phe Pro Leu Thr Glu Ala Pro Pro Gly Tyr Asp Ser Val His
                520                 525                 530

GGA GTT TCA CAA ACA GCC TCT GTC ACC ACA GAC TTT GAG GAT GAT GAA      1747
Gly Val Ser Gln Thr Ala Ser Val Thr Thr Asp Phe Glu Asp Asp Glu
            535                 540                 545

TTT GTT GTC TAT AAA ACC AAT CAG GTT AAA ATG AAA TAT ATT ATT AAA      1795
Phe Val Val Tyr Lys Thr Asn Gln Val Lys Met Lys Tyr Ile Ile Lys
        550                 555                 560

TTT TCC ATG CCT GGA GAT CAG ATA AAG GAC TTT CAT CCT AGT GAT CAT      1843
Phe Ser Met Pro Gly Asp Gln Ile Lys Asp Phe His Pro Ser Asp His
    565                 570                 575

ACT GAA TTA GAG GAA TAC AGA CCT GAG TTT TCA AAT TTT TCA AAG GTT      1891
Thr Glu Leu Glu Glu Tyr Arg Pro Glu Phe Ser Asn Phe Ser Lys Val
580                 585                 590                 595

GAA GAT TAC CAG TTA CCA GAT GCC AAA ACT TCC AGC AGC ACC AAG GCC      1939
Glu Asp Tyr Gln Leu Pro Asp Ala Lys Thr Ser Ser Ser Thr Lys Ala
                600                 605                 610

GGC CTC CAG GAT GCC TCT GGG AAC TTG GTT CCT CTG GAG GAT GTC CAC      1987
Gly Leu Gln Asp Ala Ser Gly Asn Leu Val Pro Leu Glu Asp Val His
            615                 620                 625

ATC AAA GGG AGA ATC ATA GAC ACT GTA GCC CAG GTC ATT GTT TTT CAG      2035
Ile Lys Gly Arg Ile Ile Asp Thr Val Ala Gln Val Ile Val Phe Gln
        630                 635                 640

ACA TAC ACA AAT AAA AGT CAC GTG CCC ATT GAG GCA AAA TAT ATC TTT      2083
Thr Tyr Thr Asn Lys Ser His Val Pro Ile Glu Ala Lys Tyr Ile Phe
    645                 650                 655

CCT TTG GAT GAC AAG GCC GCT GTG TGT GGC TTC GAA GCC TTC ATC AAT      2131
Pro Leu Asp Asp Lys Ala Ala Val Cys Gly Phe Glu Ala Phe Ile Asn
660                 665                 670                 675

GGG AAG CAC ATA GTT GGA GAG ATT AAA GAG AAG GAA GAA GCC CAG CAA      2179
Gly Lys His Ile Val Gly Glu Ile Lys Glu Lys Glu Glu Ala Gln Gln
                680                 685                 690

GAG TAC CTA GAA GCC GTG ACC CAG GGC CAT GGC GCT TAC CTG ATG AGT      2227
Glu Tyr Leu Glu Ala Val Thr Gln Gly His Gly Ala Tyr Leu Met Ser
            695                 700                 705
```

```
CAG GAT GCT CCG GAC GTT TTT ACT GTA AGT GTT GGA AAC TTA CCC CCT      2275
Gln Asp Ala Pro Asp Val Phe Thr Val Ser Val Gly Asn Leu Pro Pro
        710                 715                 720

AAG GCT AAG GTT CTT ATA AAA ATT ACC TAC ATC ACA GAA CTC AGC ATC      2323
Lys Ala Lys Val Leu Ile Lys Ile Thr Tyr Ile Thr Glu Leu Ser Ile
    725                 730                 735

CTG GGC ACT GTT GGT GTC TTT TTC ATG CCC GCC ACC GTA GCA CCC TGG      2371
Leu Gly Thr Val Gly Val Phe Phe Met Pro Ala Thr Val Ala Pro Trp
740                 745                 750                 755

CAA CAG GAC AAG GCT TTG AAT GAA AAC CTT CAG GAT ACA GTA GAG AAG      2419
Gln Gln Asp Lys Ala Leu Asn Glu Asn Leu Gln Asp Thr Val Glu Lys
                760                 765                 770

ATT TGT ATA AAA GAA ATA GGA ACA AAG CAA AGC TTC TCT TTG ACT ATG      2467
Ile Cys Ile Lys Glu Ile Gly Thr Lys Gln Ser Phe Ser Leu Thr Met
            775                 780                 785

TCT ATT GAG ATG CCG TAT GTG ATT GAA TTC ATT TTC AGT GAT ACA CAT      2515
Ser Ile Glu Met Pro Tyr Val Ile Glu Phe Ile Phe Ser Asp Thr His
        790                 795                 800

GAA CTG AAA CAA AAG CGC ACA GAC TGC AAA GCT GTC ATT AGC ACC ATG      2563
Glu Leu Lys Gln Lys Arg Thr Asp Cys Lys Ala Val Ile Ser Thr Met
    805                 810                 815

GAA GGC AGC TCC TTA GAC AGC AGT GGA TTT TCT CTC CAC ATC GGT TTG      2611
Glu Gly Ser Ser Leu Asp Ser Ser Gly Phe Ser Leu His Ile Gly Leu
820                 825                 830                 835

TCT GCT GCC TAT CTC CCA AGA ATG TGG GTT GAA AAA CAT CCA GAA AAA      2659
Ser Ala Ala Tyr Leu Pro Arg Met Trp Val Glu Lys His Pro Glu Lys
                840                 845                 850

GAA AGC GAG GCT TGC ATG CTT GTC TTT CAA CCC GAT CTC GAT GTC GAC      2707
Glu Ser Glu Ala Cys Met Leu Val Phe Gln Pro Asp Leu Asp Val Asp
            855                 860                 865

CTC CCT GAC CTA GCC AGT GAG AGC GAA GTG ATT ATT TGT CTT GAC TGC      2755
Leu Pro Asp Leu Ala Ser Glu Ser Glu Val Ile Ile Cys Leu Asp Cys
        870                 875                 880

TCC AGT TCC ATG GAG GGT GTG ACA TTC TTG CAA GCC AAG CAA ATC ACC      2803
Ser Ser Ser Met Glu Gly Val Thr Phe Leu Gln Ala Lys Gln Ile Thr
    885                 890                 895

TTG CAT GCG CTG TCC TTG GTG GGT GAG AAG CAG AAA GTA AAT ATT ATC      2851
Leu His Ala Leu Ser Leu Val Gly Glu Lys Gln Lys Val Asn Ile Ile
900                 905                 910                 915

CAG TTC GGC ACA GGT TAC AAG GAG CTA TTT TCG TAT CCT AAG CAT ATC      2899
Gln Phe Gly Thr Gly Tyr Lys Glu Leu Phe Ser Tyr Pro Lys His Ile
                920                 925                 930
```

```
ACA AGC AAT ACC ACG GCA GCA GAG TTC ATC ATG TCT GCC ACA CCT ACC      2947
Thr Ser Asn Thr Thr Ala Ala Glu Phe Ile Met Ser Ala Thr Pro Thr
            935                 940                 945

ATG GGG AAC ACA GAC TTC TGG AAA ACA CTC CGA TAT CTT AGC TTA TTG      2995
Met Gly Asn Thr Asp Phe Trp Lys Thr Leu Arg Tyr Leu Ser Leu Leu
        950                 955                 960

TAC CCT GCT CGA GGG TCA CGG AAC ATC CTC CTG GTG TCT GAT GGG CAC      3043
Tyr Pro Ala Arg Gly Ser Arg Asn Ile Leu Leu Val Ser Asp Gly His
    965                 970                 975

CTC CAG GAT GAG AGC CTG ACA TTA CAG CTC GTG AAG AGG AGC CGC CCG      3091
Leu Gln Asp Glu Ser Leu Thr Leu Gln Leu Val Lys Arg Ser Arg Pro
980                 985                 990                 995

CAC ACC AGG TTA TTC GCC TGC GGT ATC GGT TCT ACA GCA AAT CGT CAC      3139
His Thr Arg Leu Phe Ala Cys Gly Ile Gly Ser Thr Ala Asn Arg His
                1000                1005                1010

GTC TTA AGG ATT TTG TCC CAG TGT GGT GCC GGA GTA TTT GAA TAT TTT      3187
Val Leu Arg Ile Leu Ser Gln Cys Gly Ala Gly Val Phe Glu Tyr Phe
            1015                1020                1025

AAT GCA AAA TCC AAG CAT AGT TGG AGA AAA CAG ATA GAA GAC CAA ATG      3235
Asn Ala Lys Ser Lys His Ser Trp Arg Lys Gln Ile Glu Asp Gln Met
        1030                1035                1040

ACC AGG CTA TGT TCT CCG AGT TGC CAC TCT GTC TCC GTC AAA TGG CAG      3283
Thr Arg Leu Cys Ser Pro Ser Cys His Ser Val Ser Val Lys Trp Gln
    1045                1050                1055

CAA CTC AAT CCA GAT GCG CCC GAG GCC CTG CAG GCC CCA GCC CAG GTG      3331
Gln Leu Asn Pro Asp Ala Pro Glu Ala Leu Gln Ala Pro Ala Gln Val
1060                1065                1070                1075

CCA TCC TTG TTT CGC AAT GAT CGA CTC CTT GTC TAT GGA TTC ATT CCT      3379
Pro Ser Leu Phe Arg Asn Asp Arg Leu Leu Val Tyr Gly Phe Ile Pro
                1080                1085                1090

CAC TGC ACA CAA GCA ACT CTG TGT GCA CTA ATT CAA GAG AAA GAA TTT      3427
His Cys Thr Gln Ala Thr Leu Cys Ala Leu Ile Gln Glu Lys Glu Phe
            1095                1100                1105

TGT ACA ATG GTG TCG ACT ACT GAG CTT CAG AAG ACA ACT GGA ACT ATG      3475
Cys Thr Met Val Ser Thr Thr Glu Leu Gln Lys Thr Thr Gly Thr Met
        1110                1115                1120

ATC CAC AAG CTG GCA GCC CGA GCT CTA ATC AGA GAT TAT GAA GAT GGC      3523
Ile His Lys Leu Ala Ala Arg Ala Leu Ile Arg Asp Tyr Glu Asp Gly
    1125                1130                1135

ATT CTT CAC GAA AAT GAA ACC AGT CAT GAG ATG AAA AAA CAA ACC TTG      3571
Ile Leu His Glu Asn Glu Thr Ser His Glu Met Lys Lys Gln Thr Leu
1140                1145                1150                1155
```

```
AAA TCT CTG ATT ATT AAA CTC AGT AAA GAA AAC TCT CTC ATA ACA CAA      3619
Lys Ser Leu Ile Ile Lys Leu Ser Lys Glu Asn Ser Leu Ile Thr Gln
                1160                1165                1170

TTT ACA AGC TTT GTG GCA GTT GAG AAA AGG GAT GAG AAT GAG TCG CCT      3667
Phe Thr Ser Phe Val Ala Val Glu Lys Arg Asp Glu Asn Glu Ser Pro
            1175                1180                1185

TTT CCT GAT ATT CCA AAA GTT TCT GAA CTT ATT GCC AAA GAA GAT GTA      3715
Phe Pro Asp Ile Pro Lys Val Ser Glu Leu Ile Ala Lys Glu Asp Val
        1190                1195                1200

GAC TTC CTG CCC TAC ATG AGC TGG CAG GGG GAG CCC CAA GAA GCC GTC      3763
Asp Phe Leu Pro Tyr Met Ser Trp Gln Gly Glu Pro Gln Glu Ala Val
    1205                1210                1215

AGG AAC CAG TCT CTT TTA GCA TCC TCT GAG TGG CCA GAA TTA CGT TTA      3811
Arg Asn Gln Ser Leu Leu Ala Ser Ser Glu Trp Pro Glu Leu Arg Leu
1220                1225                1230                1235

TCC AAA CGA AAA CAT AGG AAA ATT CCA TTT TCC AAA AGA AAA ATG GAA      3859
Ser Lys Arg Lys His Arg Lys Ile Pro Phe Ser Lys Arg Lys Met Glu
                1240                1245                1250

TTA TCT CAG CCA GAA GTT TCT GAA GAT TTT GAA GAG GAT GGC TTA GGT      3907
Leu Ser Gln Pro Glu Val Ser Glu Asp Phe Glu Glu Asp Gly Leu Gly
            1255                1260                1265

GTA CTA CCA GCT TTC ACA TCA AAT TTG GAA CGT GGA GGT GTG GAA AAG      3955
Val Leu Pro Ala Phe Thr Ser Asn Leu Glu Arg Gly Gly Val Glu Lys
        1270                1275                1280

CTA TTG GAT TTA AGT TGG ACA GAG TCA TGT AAA CCA ACA GCA ACT GAA      4003
Leu Leu Asp Leu Ser Trp Thr Glu Ser Cys Lys Pro Thr Ala Thr Glu
    1285                1290                1295

CCA CTA TTT AAG AAA GTC AGT CCA TGG GAA ACA TCT ACT TCT AGC TTT      4051
Pro Leu Phe Lys Lys Val Ser Pro Trp Glu Thr Ser Thr Ser Ser Phe
1300                1305                1310                1315

TTT CCT ATT TTG GCT CCG GCC GTT GGT TCC TAT CTT ACC CCG ACT ACC      4099
Phe Pro Ile Leu Ala Pro Ala Val Gly Ser Tyr Leu Thr Pro Thr Thr
                1320                1325                1330

CGC GCT CAC AGT CCT GCT TCC TTG TCT TTT GCC TCA TAT CGT CAG GTA      4147
Arg Ala His Ser Pro Ala Ser Leu Ser Phe Ala Ser Tyr Arg Gln Val
            1335                1340                1345

GCT AGT TTC GGT TCA GCT GCT CCT CCC AGA CAG TTT GAT GCA TCT CAA      4195
Ala Ser Phe Gly Ser Ala Ala Pro Pro Arg Gln Phe Asp Ala Ser Gln
        1350                1355                1360

TTC AGC CAA GGC CCT GTG CCT GGC ACT TGT GCT GAC TGG ATC CCA CAG      4243
Phe Ser Gln Gly Pro Val Pro Gly Thr Cys Ala Asp Trp Ile Pro Gln
    1365                1370                1375
```

```
TCG GCG TCT TGT CCC ACA GGA CCT CCC CAG AAC CCA CCT TCT GCA CCC      4291
Ser Ala Ser Cys Pro Thr Gly Pro Pro Gln Asn Pro Pro Ser Ala Pro
1380                 1385                 1390                 1395

TAT TGT GGC ATT GTT TTT TCA GGG AGC TCA TTA AGC TCT GCA CAG TCT      4339
Tyr Cys Gly Ile Val Phe Ser Gly Ser Ser Leu Ser Ser Ala Gln Ser
                1400                 1405                 1410

GCT CCA CTG CAA CAT CCT GGA GGC TTT ACT ACC AGG CCT TCT GCT GGC      4387
Ala Pro Leu Gln His Pro Gly Gly Phe Thr Thr Arg Pro Ser Ala Gly
            1415                 1420                 1425

ACC TTC CCT GAG CTG GAT TCT CCC CAG CTT CAT TTC TCT CTT CCT ACA      4435
Thr Phe Pro Glu Leu Asp Ser Pro Gln Leu His Phe Ser Leu Pro Thr
        1430                 1435                 1440

GAC CCT GAT CCC ATC AGA GGT TTT GGG TCT TAT CAT CCC TCT GCT TAC      4483
Asp Pro Asp Pro Ile Arg Gly Phe Gly Ser Tyr His Pro Ser Ala Tyr
    1445                 1450                 1455

TCT CCT TTT CAT TTT CAA CCT TCC GCA GCC TCT TTG ACT GCC AAC CTT      4531
Ser Pro Phe His Phe Gln Pro Ser Ala Ala Ser Leu Thr Ala Asn Leu
1460                 1465                 1470                 1475

AGG CTG CCA ATG GCC TCT GCT TTA CCT GAG GCT CTT TGC AGT CAG TCC      4579
Arg Leu Pro Met Ala Ser Ala Leu Pro Glu Ala Leu Cys Ser Gln Ser
                1480                 1485                 1490

CGG ACT ACC CCA GTA GAT CTC TGT CTT CTA GAA GAA TCA GTA GGC AGT      4627
Arg Thr Thr Pro Val Asp Leu Cys Leu Leu Glu Glu Ser Val Gly Ser
            1495                 1500                 1505

CTC GAA GGA AGT CGA TGT CCT GTC TTT GCT TTT CAA AGT TCT GAC ACA      4675
Leu Glu Gly Ser Arg Cys Pro Val Phe Ala Phe Gln Ser Ser Asp Thr
        1510                 1515                 1520

GAA AGT GAT GAG CTA TCA GAA GTA CTT CAA GAC AGC TGC TTT TTA CAA      4723
Glu Ser Asp Glu Leu Ser Glu Val Leu Gln Asp Ser Cys Phe Leu Gln
    1525                 1530                 1535

ATA AAG TGT GAT ACA AAA GAT GAC AGT ATC CCG TGC TTT CTG GAA TTA      4771
Ile Lys Cys Asp Thr Lys Asp Asp Ser Ile Pro Cys Phe Leu Glu Leu
1540                 1545                 1550                 1555

AAA GAA GAG GAT GAA ATA GTG TGC ACA CAA CAC TGG CAG GAT GCT GTG      4819
Lys Glu Glu Asp Glu Ile Val Cys Thr Gln His Trp Gln Asp Ala Val
                1560                 1565                 1570

CCT TGG ACA GAA CTC CTC AGT CTA CAG ACA GAG GAT GGC TTC TGG AAA      4867
Pro Trp Thr Glu Leu Leu Ser Leu Gln Thr Glu Asp Gly Phe Trp Lys
            1575                 1580                 1585

CTT ACA CCA GAA CTG GGA CTT ATA TTA AAT CTT AAT ACA AAT GGT TTG      4915
Leu Thr Pro Glu Leu Gly Leu Ile Leu Asn Leu Asn Thr Asn Gly Leu
        1590                 1595                 1600
```

```
CAC AGC TTT CTT AAA CAA AAA GGC ATT CAA TCT CTA GGT GTA AAA GGA      4963
His Ser Phe Leu Lys Gln Lys Gly Ile Gln Ser Leu Gly Val Lys Gly
    1605                1610                1615

AGA GAA TGT CTC CTG GAC CTA ATT GCC ACA ATG CTG GTA CTA CAG TTT      5011
Arg Glu Cys Leu Leu Asp Leu Ile Ala Thr Met Leu Val Leu Gln Phe
1620                1625                1630                1635

ATT CGC ACC AGG TTG GAA AAA GAG GGA ATA GTG TTC AAA TCA CTG ATG      5059
Ile Arg Thr Arg Leu Glu Lys Glu Gly Ile Val Phe Lys Ser Leu Met
                1640                1645                1650

AAA ATG GAT GAC CCT TCT ATT TCC AGG AAT ATT CCC TGG GCT TTT GAG      5107
Lys Met Asp Asp Pro Ser Ile Ser Arg Asn Ile Pro Trp Ala Phe Glu
            1655                1660                1665

GCA ATA AAG CAA GCA AGT GAA TGG GTA AGA AGA ACT GAA GGA CAG TAC      5155
Ala Ile Lys Gln Ala Ser Glu Trp Val Arg Arg Thr Glu Gly Gln Tyr
        1670                1675                1680

CCA TCT ATC TGC CCA CGG CTT GAA CTG GGG AAC GAC TGG GAC TCT GCC      5203
Pro Ser Ile Cys Pro Arg Leu Glu Leu Gly Asn Asp Trp Asp Ser Ala
    1685                1690                1695

ACC AAG CAG TTG CTG GGA CTC CAG CCC ATA AGC ACT GTG TCC CCT CTT      5251
Thr Lys Gln Leu Leu Gly Leu Gln Pro Ile Ser Thr Val Ser Pro Leu
1700                1705                1710                1715

CAT AGA GTC CTC CAT TAC AGT CAA GGC TAAGTCAAAT GAAACTGAAT TTTAA      5303
His Arg Val Leu His Tyr Ser Gln Gly
                1720

ACTTTTTGCA TGCTTCTATG TAGAAAATAA TCAAATGATA ATAGATAATT ATAATGAAAC    5363

TTCATTAAGG TTTCATTCAG TGTAGCAATT ACTGTCTTTA AAAATTAAGT GGAAGAAGAA    5423

TTACTTTAAT CAACTAACAA GCAATAATAA AATGAAACTT AAAATAAAAA AAAAAAAAAA    5483

AAAAAAA                                                              5490
```

(2) INFORMATION FOR SEQ ID NO:2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1724 amino acids

(B) TYPE: amino acid

(C) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(ix) SEQUENCE DESCRIPTION: SEQ ID NO:2:

```
Met Val Met Gly Ile Phe Ala Asn Cys Ile Phe Cys Leu Lys Val Lys Tyr Leu
  1               5                  10                  15

Pro Gln Gln Gln Lys Lys Lys Leu Gln Thr Asp Ile Lys Glu Asn Gly Gly Lys
     20                  25                  30                  35
```

Phe Ser Phe Ser Leu Asn Pro Gln Cys Thr His Ile Ile Leu Asp Asn Ala Asp
40 45 50

Val Leu Ser Gln Tyr Gln Leu Asn Ser Ile Gln Lys Asn His Val His Ile Ala
55 60 65 70

Asn Pro Asp Phe Ile Trp Lys Ser Ile Arg Glu Lys Arg Leu Leu Asp Val Lys
75 80 85 90

Asn Tyr Asp Pro Tyr Lys Pro Leu Asp Ile Thr Pro Pro Pro Asp Gln Lys Ala
95 100 105

Ser Ser Ser Glu Val Lys Thr Glu Gly Leu Cys Pro Asp Ser Ala Thr Glu Glu
110 115 120 125

Glu Asp Thr Val Glu Leu Thr Glu Phe Gly Met Gln Asn Val Glu Ile Phe His
130 135 140

Leu Pro Gln Asp Phe Glu Val Ala Lys Tyr Asn Thr Leu Glu Lys Val Gly Met
145 150 155 160

Glu Gly Gly Gln Glu Ala Val Val Val Glu Leu Gln Cys Ser Arg Asp Ser Arg
165 170 175 180

Asp Cys Pro Phe Leu Ile Ser Ser His Phe Leu Leu Asp Asp Gly Met Glu Thr
185 190 195

Arg Arg Gln Phe Ala Ile Lys Lys Thr Ser Glu Asp Ala Ser Glu Tyr Phe Glu
200 205 210 215

Asn Tyr Ile Glu Glu Leu Lys Lys Gln Gly Phe Leu Leu Arg Glu His Phe Thr
220 225 230

Pro Glu Ala Thr Gln Leu Ala Ser Glu Gln Leu Gln Ala Leu Leu Leu Glu Glu
235 240 245 250

Val Met Asn Ser Ser Thr Leu Ser Gln Glu Val Ser Asp Leu Val Glu Met Ile
255 260 265 270

Trp Ala Glu Ala Leu Gly His Leu Glu His Met Leu Leu Lys Pro Val Asn Arg
275 280 285

Ile Ser Leu Asn Asp Val Ser Lys Ala Glu Gly Ile Leu Leu Leu Val Lys Ala
290 295 300 305

Ala Leu Lys Asn Gly Glu Thr Ala Glu Gln Leu Gln Lys Met Met Thr Glu Phe
310 315 320

Tyr Arg Leu Ile Pro His Lys Gly Thr Met Pro Lys Glu Val Asn Leu Gly Leu
325 330 335 340

Leu Ala Lys Lys Ala Asp Leu Cys Gln Leu Ile Arg Asp Met Val Asn Val Cys
345 350 355 360

Glu Thr Asn Leu Ser Lys Pro Asn Pro Pro Ser Leu Ala Lys Tyr Arg Ala Leu
365 370 375

Arg Cys Lys Ile Glu His Val Glu Gln Asn Thr Glu Glu Phe Leu Arg Val Arg
380 385 390 395

Lys Glu Val Leu Gln Asn His His Ser Lys Ser Pro Val Asp Val Leu Gln Ile
400 405 410

Phe Arg Val Gly Arg Val Asn Glu Thr Thr Glu Phe Leu Ser Lys Leu Gly Asn
415 420 425 430

Val Arg Pro Leu Leu His Gly Ser Pro Val Gln Asn Ile Val Gly Ile Leu Cys
435 440 445 450

Arg Gly Leu Leu Leu Pro Lys Val Val Glu Asp Arg Gly Val Gln Arg Thr Asp
455 460 465

Val Gly Asn Leu Gly Ser Gly Ile Tyr Phe Ser Asp Ser Leu Ser Thr Ser Ile
470 475 480 485

Lys Tyr Ser His Pro Gly Glu Thr Asp Gly Thr Arg Leu Leu Leu Ile Cys Asp
490 495 500

Val Ala Leu Gly Lys Cys Met Asp Leu His Glu Lys Asp Phe Pro Leu Thr Glu
505 510 515 520

Ala Pro Pro Gly Tyr Asp Ser Val His Gly Val Ser Gln Thr Ala Ser Val Thr
525 530 535 540

Thr Asp Phe Glu Asp Asp Glu Phe Val Val Tyr Lys Thr Asn Gln Val Lys Met
545 550 555

Lys Tyr Ile Ile Lys Phe Ser Met Pro Gly Asp Gln Ile Lys Asp Phe His Pro
560 565 570 575

Ser Asp His Thr Glu Leu Glu Glu Tyr Arg Pro Glu Phe Ser Asn Phe Ser Lys
580 585 590

Val Glu Asp Tyr Gln Leu Pro Asp Ala Lys Thr Ser Ser Ser Thr Lys Ala Gly
595 600 605 610

Leu Gln Asp Ala Ser Gly Asn Leu Val Pro Leu Glu Asp Val His Ile Lys Gly
615 620 625 630

Arg Ile Ile Asp Thr Val Ala Gln Val Ile Val Phe Gln Thr Tyr Thr Asn Lys
635 640 645

Ser His Val Pro Ile Glu Ala Lys Tyr Ile Phe Pro Leu Asp Asp Lys Ala Ala
650 655 660 665

Val Cys Gly Phe Glu Ala Phe Ile Asn Gly Lys His Ile Val Gly Glu Ile Lys
670 675 680

Glu Lys Glu Glu Ala Gln Gln Glu Tyr Leu Glu Ala Val Thr Gln Gly His Gly
685 690 695 700

Ala Tyr Leu Met Ser Gln Asp Ala Pro Asp Val Phe Thr Val Ser Val Gly Asn
705 710 715 720

Leu Pro Pro Lys Ala Lys Val Leu Ile Lys Ile Thr Tyr Ile Thr Glu Leu Ser
725 730 735

Ile Leu Gly Thr Val Gly Val Phe Phe Met Pro Ala Thr Val Ala Pro Trp Gln
740 745 750 755

Gln Asp Lys Ala Leu Asn Glu Asn Leu Gln Asp Thr Val Glu Lys Ile Cys Ile
760 765 770

Lys Glu Ile Gly Thr Lys Gln Ser Phe Ser Leu Thr Met Ser Ile Glu Met Pro
775 780 785 790

Tyr Val Ile Glu Phe Ile Phe Ser Asp Thr His Glu Leu Lys Gln Lys Arg Thr
795 800 805 810

Asp Cys Lys Ala Val Ile Ser Thr Met Glu Gly Ser Ser Leu Asp Ser Ser Gly
815 820 825

Phe Ser Leu His Ile Gly Leu Ser Ala Ala Tyr Leu Pro Arg Met Trp Val Glu
830 835 840 845

Lys His Pro Glu Lys Glu Ser Glu Ala Cys Met Leu Val Phe Gln Pro Asp Leu
850 855 860

Asp Val Asp Leu Pro Asp Leu Ala Ser Glu Ser Glu Val Ile Ile Cys Leu Asp
865 870 875 880

Cys Ser Ser Ser Met Glu Gly Val Thr Phe Leu Gln Ala Lys Gln Ile Thr Leu
885 890 895 900

His Ala Leu Ser Leu Val Gly Glu Lys Gln Lys Val Asn Ile Ile Gln Phe Gly
905 910 915

Thr Gly Tyr Lys Glu Leu Phe Ser Tyr Pro Lys His Ile Thr Ser Asn Thr Thr
920 925 930 935

Ala Ala Glu Phe Ile Met Ser Ala Thr Pro Thr Met Gly Asn Thr Asp Phe Trp
940 945 950

Lys Thr Leu Arg Tyr Leu Ser Leu Leu Tyr Pro Ala Arg Gly Ser Arg Asn Ile
955 960 965 970

Leu Leu Val Ser Asp Gly His Leu Gln Asp Glu Ser Leu Thr Leu Gln Leu Val
975 980 985 990

Lys Arg Ser Arg Pro His Thr Arg Leu Phe Ala Cys Gly Ile Gly Ser Thr Ala
995 1000 1005

Asn Arg His Val Leu Arg Ile Leu Ser Gln Cys Gly Ala Gly Val Phe Glu Tyr
1010 1015 1020 1025

Phe Asn Ala Lys Ser Lys His Ser Trp Arg Lys Gln Ile Glu Asp Gln Met Thr
1030 1035 1040

Arg Leu Cys Ser Pro Ser Cys His Ser Val Ser Val Lys Trp Gln Gln Leu Asn
1045 1050 1055 1060

Pro Asp Ala Pro Glu Ala Leu Gln Ala Pro Ala Gln Val Pro Ser Leu Phe Arg
1065 1070 1075 1080

Asn Asp Arg Leu Leu Val Tyr Gly Phe Ile Pro His Cys Thr Gln Ala Thr Leu
1085 1090 1095

Cys Ala Leu Ile Gln Glu Lys Glu Phe Cys Thr Met Val Ser Thr Thr Glu Leu
1100 1105 1110 1115

Gln Lys Thr Thr Gly Thr Met Ile His Lys Leu Ala Ala Arg Ala Leu Ile Arg
1120 1125 1130

Asp Tyr Glu Asp Gly Ile Leu His Glu Asn Glu Thr Ser His Glu Met Lys Lys
1135 1140 1145 1150

Gln Thr Leu Lys Ser Leu Ile Ile Lys Leu Ser Lys Glu Asn Ser Leu Ile Thr
1155 1160 1165 1170

Gln Phe Thr Ser Phe Val Ala Val Glu Lys Arg Asp Glu Asn Glu Ser Pro Phe
1175 1180 1185

Pro Asp Ile Pro Lys Val Ser Glu Leu Ile Ala Lys Glu Asp Val Asp Phe Leu
1190 1195 1200 1205

Pro Tyr Met Ser Trp Gln Gly Glu Pro Gln Glu Ala Val Arg Asn Gln Ser Leu
1210 1215 1220

Leu Ala Ser Ser Glu Trp Pro Glu Leu Arg Leu Ser Lys Arg Lys His Arg Lys
1225 1230 1235 1240

Ile Pro Phe Ser Lys Arg Lys Met Glu Leu Ser Gln Pro Glu Val Ser Glu Asp
1245 1250 1255 1260

Phe Glu Glu Asp Gly Leu Gly Val Leu Pro Ala Phe Thr Ser Asn Leu Glu Arg
1265 1270 1275

Gly Gly Val Glu Lys Leu Leu Asp Leu Ser Trp Thr Glu Ser Cys Lys Pro Thr
1280 1285 1290 1295

Ala Thr Glu Pro Leu Phe Lys Lys Val Ser Pro Trp Glu Thr Ser Thr Ser Ser
1300 1305 1310

Phe Phe Pro Ile Leu Ala Pro Ala Val Gly Ser Tyr Leu Thr Pro Thr Thr Arg
1315 1320 1325 1330

Ala His Ser Pro Ala Ser Leu Ser Phe Ala Ser Tyr Arg Gln Val Ala Ser Phe
1335 1340 1345 1350

Gly Ser Ala Ala Pro Pro Arg Gln Phe Asp Ala Ser Gln Phe Ser Gln Gly Pro
1355 1360 1365

Val Pro Gly Thr Cys Ala Asp Trp Ile Pro Gln Ser Ala Ser Cys Pro Thr Gly
1370 1375 1380 1385

Pro Pro Gln Asn Pro Pro Ser Ala Pro Tyr Cys Gly Ile Val Phe Ser Gly Ser
1390 1395 1400

Ser Leu Ser Ser Ala Gln Ser Ala Pro Leu Gln His Pro Gly Gly Phe Thr Thr
1405 1410 1415 1420

Arg Pro Ser Ala Gly Thr Phe Pro Glu Leu Asp Ser Pro Gln Leu His Phe Ser
1425 1430 1435 1440

Leu Pro Thr Asp Pro Asp Pro Ile Arg Gly Phe Gly Ser Tyr His Pro Ser Ala
1445 1450 1455

Tyr Ser Pro Phe His Phe Gln Pro Ser Ala Ala Ser Leu Thr Ala Asn Leu Arg
1460 1465 1470 1475

Leu Pro Met Ala Ser Ala Leu Pro Glu Ala Leu Cys Ser Gln Ser Arg Thr Thr
1480 1485 1490

Pro Val Asp Leu Cys Leu Leu Glu Glu Ser Val Gly Ser Leu Glu Gly Ser Arg
1495 1500 1505 1510

Cys Pro Val Phe Ala Phe Gln Ser Ser Asp Thr Glu Ser Asp Glu Leu Ser Glu
1515 1520 1525 1530

Val Leu Gln Asp Ser Cys Phe Leu Gln Ile Lys Cys Asp Thr Lys Asp Asp Ser
1535 1540 1545

Ile Pro Cys Phe Leu Glu Leu Lys Glu Glu Asp Glu Ile Val Cys Thr Gln His
1550 1555 1560 1565

Trp Gln Asp Ala Val Pro Trp Thr Glu Leu Leu Ser Leu Gln Thr Glu Asp Gly
1570 1575 1580

Phe Trp Lys Leu Thr Pro Glu Leu Gly Leu Ile Leu Asn Leu Asn Thr Asn Gly
1585 1590 1595 1600

Leu His Ser Phe Leu Lys Gln Lys Gly Ile Gln Ser Leu Gly Val Lys Gly Arg
1605 1610 1615 1620

Glu Cys Leu Leu Asp Leu Ile Ala Thr Met Leu Val Leu Gln Phe Ile Arg Thr
1625 1630 1635

Arg Leu Glu Lys Glu Gly Ile Val Phe Lys Ser Leu Met Lys Met Asp Asp Pro
1640 1645 1650 1655

Ser Ile Ser Arg Asn Ile Pro Trp Ala Phe Glu Ala Ile Lys Gln Ala Ser Glu
1660 1665 1670

Trp Val Arg Arg Thr Glu Gly Gln Tyr Pro Ser Ile Cys Pro Arg Leu Glu Leu
1675 1680 1685 1690

Gly Asn Asp Trp Asp Ser Ala Thr Lys Gln Leu Leu Gly Leu Gln Pro Ile Ser
1695 1700 1705 1710

Thr Val Ser Pro Leu His Arg Val Leu His Tyr Ser Gln Gly
1715 1720

WE CLAIM:

1. A protein consisting essentially of purified human minor vault protein p193 or purified biologically active variants thereof, or a combination of purified human minor vault protein p193 and biologically active variants thereof.

2. A recombinant protein according to claim 1.

3. A protein of claim 1, having an amino acid sequence of greater than about 50% identity of the amino acid sequence as set forth in Figure 2, SEQ ID NO:2.

4. The protein of claim 1, having an amino acid as set forth in SEQ ID NO:2.

5. A protein recognized by a monoclonal antibody having affinity to the protein of claim 1.

6. A polynucleotide molecule encoding a protein according to claim 1, or its complementary strands.

7. A polynucleotide molecule which hybridizes to a polynucleotide sequence according to claim 6, or its complementary strands.

8. An RNA molecule according to claim 6.

9. A DNA molecule according to claim 6.

10. A purified and isolated polynucleotide molecule consisting essentially of a nucleotide sequence encoding human minor vault protein p193, or its complementary strands, or a combination of a nucleotide sequence encoding human minor vault protein p193 and its complementary strands.

11. A polynucleotide molecule which hybridizes to a polynucleotide sequence according to claim 10, or its complementary strands.

12. An RNA molecule according to claim 10.

13. A DNA molecule according to claim 10.

14. A vector containing the polynucleotide of claim 6.

15. A prokaryotic or eukaryotic host cell stably transformed or transfected by the vector of claim 14.

16. A vector containing the polynucleotide of claim 8.

17. A prokaryotic or eukaryotic host cell stably transformed or transfected by the vector of claim 16.

18. A vector containing a DNA molecule encoding human minor vault protein p193.

19. A prokaryotic or eukaryotic host cell stably transformed or transfected by the vector of claim 18.

20. A high affinity monoclonal antibody which immunoreacts with a protein according to claim 1.

21. The antibody of claim 20 having an Fc portion selected from the group consisting of the IgM class, the IgG class and the IgA class.

22. A high affinity monoclonal antibody which immunoreacts with human minor vault protein p193.

23. The antibody of claim 22 having an Fc portion selected from the group consisting of the IgM class, the IgG class and the IgA class.

24. A method of making a monoclonal antibody which immunoreacts with human minor vault protein p193 comprising the steps of:

(a) administering human minor vault protein p193 to a host in an amount sufficient to induce the production of antibodies to the human minor vault protein p193 from the antibody-producing cells;

(b) recovering the antibody-producing cells from the host;

(c) forming cell hybrids by fusing the antibody-producing cell to cells capable of substantially unlimited reproduction;

(d) culturing the hybrids; and

(e) collecting the monoclonal antibodies as a product of the hybrids.

25. The method of claim 24, wherein the cells capable of substantially unlimited reproduction in step (c) are myeloma cells.

26. A method of making a protein of claim 1, comprising the steps of:

(a) culturing a microorganism transformed with a polynucleotide encoding human minor vault protein p193; and

(b) recovering the human minor vault protein p193.

27. A method of diagnosing a patient with a multidrug-resistant cancer comprising the steps of:

(a) providing a sample of tissue or fluid from the patient;

(b) determining the level of a substance selected from the group consisting of p193 protein, p193 DNA, p193 mRNA, a substantial portion of p193 protein, a

substantial portion of p193 DNA, a substantial portion of p193 mRNA and a combination of one of the foregoing in the patient sample; and

(c) comparing the level of the substance determined in step (b) to a known range of levels for the substance in patients with multidrug-resistant cancers,

wherein a diagnosis of multidrug-resistant cancer is made when the level of the substance determined in step (b) is within the range of levels for the substance in patients with multidrug-resistant cancers.

28. The method of claim 27, wherein the sample is selected from the group consisting of bone marrow, cerebral spinal fluid, blood, tears, saliva and a biopsy specimen.

29. A method of treating a patient with multidrug-resistant cancer comprising the steps of:

(a) diagnosing a patient with multidrug-resistant cancer according to claim 27; and

(b) treating the patient.

30. The method of claim 29, wherein the treating step (b) comprises administering to the patient antibodies having an affinity for a substance selected from the group consisting of p193 protein and a polynucleotide encoding p193.

31. The method of claim 29, wherein the treating step (b) comprises administering to the patient at least one antisense polynucleotide having an affinity for a polynucleotide encoding p193.

32. The method of claim 29, wherein the treating step (b) comprises administering to the patient at least one drug that blocks NAD.

33. The method of claim 30, wherein the drug is selected from the group consisting of PD128763 and 3-aminobenzamide.

34. A method of treating a patient with multidrug-resistant cancer comprising the step of administering to the patient antibodies having an affinity for a substance selected from the group consisting of p193 protein and a polynucleotide encoding p193.

35. A method of treating a patient with multidrug-resistant cancer comprising the step of administering to the patient at least one antisense polynucleotide having an affinity for a polynucleotide encoding p193.

36. A method of treating a patient with multidrug-resistant cancer comprising the

step of administering to the patient at least one drug that blocks NAD.

37. The method of claim 36, wherein the drug is selected from the group consisting of PD128763 and 3-aminobenzamide.

# FIG. 1a

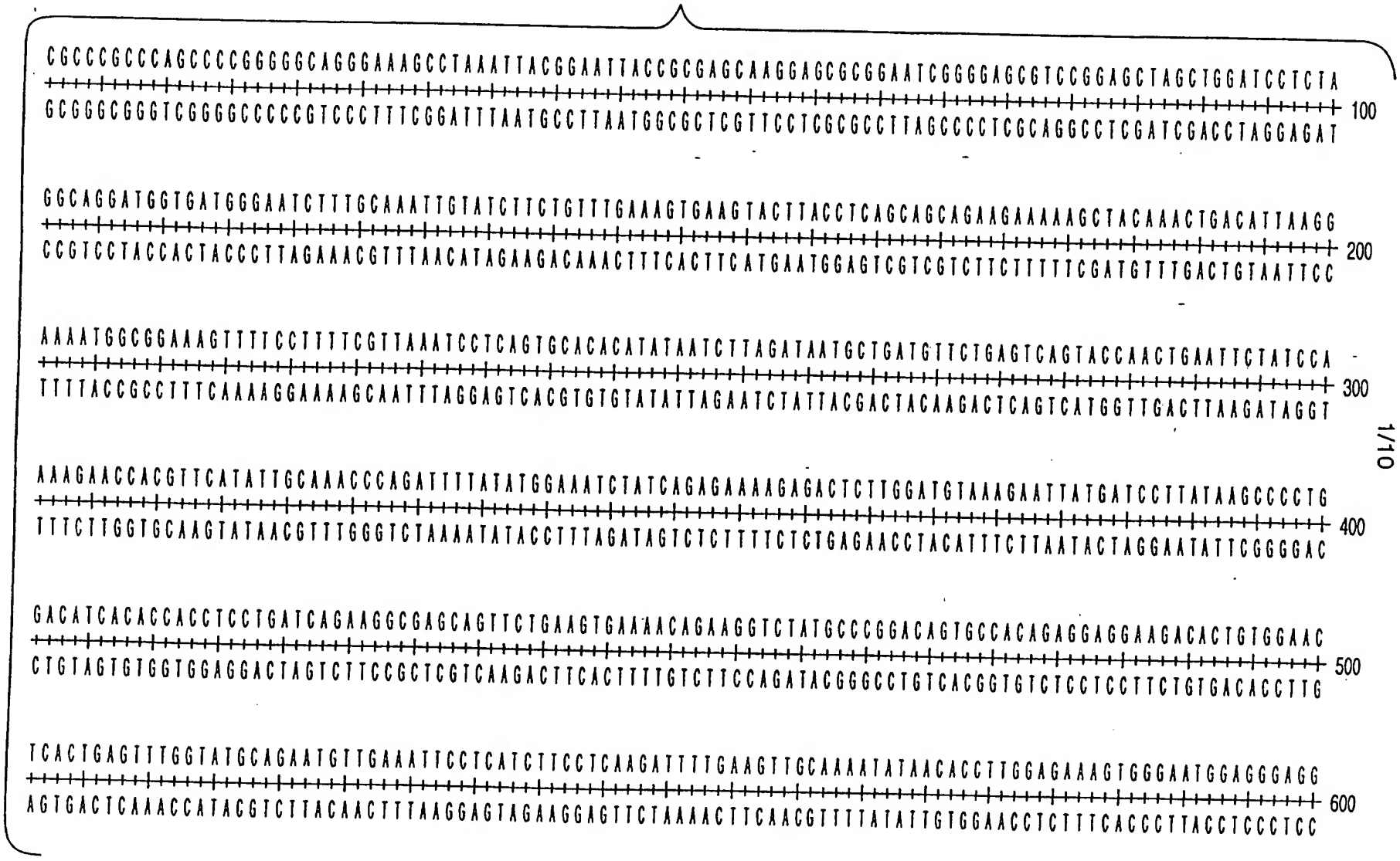

CGCCCGCCCAGCCCCGGGGGCAGGGAAAGCCTAAATTACGGAATTACCGCGAGCAAGGAGCGCGGAATCGGGGAGCGTCCGGAGCTAGCTGGATCCTCTA
GCGGGCGGGTCGGGGCCCCCGTCCCTTTCGGATTTAATGCCTTAATGGCGCTCGTTCCTCGCGCCTTAGCCCCTCGCAGGCCTCGATCGACCTAGGAGAT
100
GGCAGGATGGTGATGGGAATCTTTGCAAATTGTATCTTCTGTTTGAAAGTGAAGTACTTACCTCAGCAGCAGAAGAAAAAGCTACAAACTGACATTAAGG
CCGTCCTACCACTACCCTTAGAAACGTTTAACATAGAAGACAAACTTTCACTTCATGAATGGAGTCGTCGTCTTCTTTTTCGATGTTTGACTGTAATTCC
200
AAAATGGCGGAAAGTTTTCCTTTTCGTTAAATCCTCAGTGCACACATATAATCTTAGATAATGCTGATGTTCTGAGTCAGTACCAACTGAATTCTATCCA
TTTTACCGCCTTTCAAAAGGAAAAGCAATTTAGGAGTCACGTGTGTATATTAGAATCTATTACGACTACAAGACTCAGTCATGGTTGACTTAAGATAGGT
300
AAAGAACCACGTTCATATTGCAAACCCAGATTTTATATGGAAATCTATCAGAGAAAAGAGACTCTTGGATGTAAAGAATTATGATCCTTATAAGCCCCTG
TTTCTTGGTGCAAGTATAACGTTTGGGTCTAAAATATACCTTTAGATAGTCTCTTTTCTCTGAGAACCTACATTTCTTAATACTAGGAATATTCGGGGAC
400
GACATCACACCACCTCCTGATCAGAAGGCGAGCAGTTCTGAAGTGAAAACAGAAGGTCTATGCCCGGACAGTGCCACAGAGGAGGAAGACACTGTGGAAC
CTGTAGTGTGGTGGAGGACTAGTCTTCCGCTCGTCAAGACTTCACTTTTGTCTTCCAGATACGGGCCTGTCACGGTGTCTCCTCCTTCTGTGACACCTTG
500
TCACTGAGTTTGGTATGCAGAATGTTGAAATTCCTCATCTTCCTCAAGATTTTGAAGTTGCAAAATATAACACCTTGGAGAAAGTGGGAATGGAGGGAGG
AGTGACTCAAACCATACGTCTTACAACTTTAAGGAGTAGAAGGAGTTCTAAAACTTCAACGTTTTATATTGTGGAACCTCTTTCACCCTTACCTCCCTCC
600

FIG. 1b

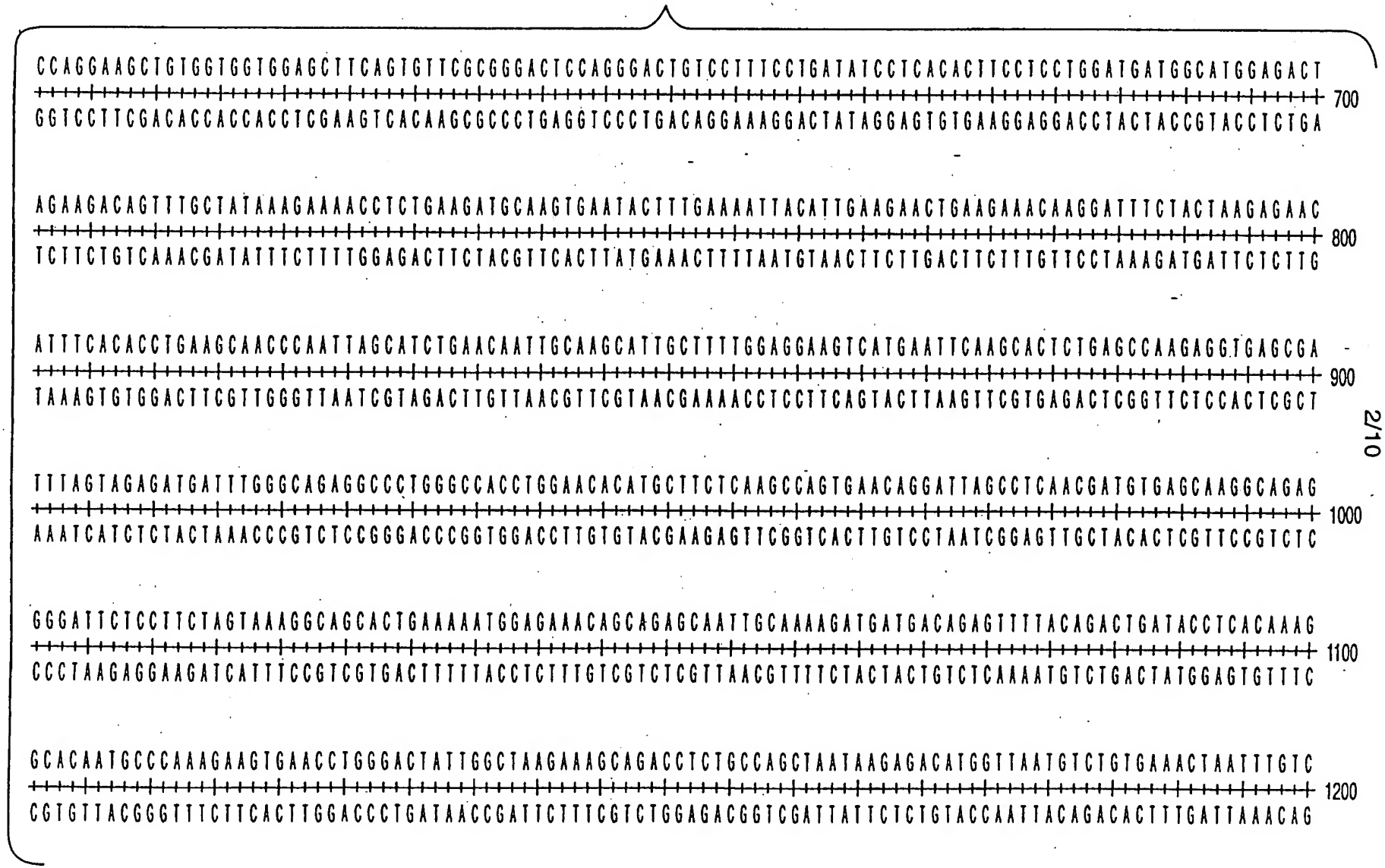


FIG. 1c

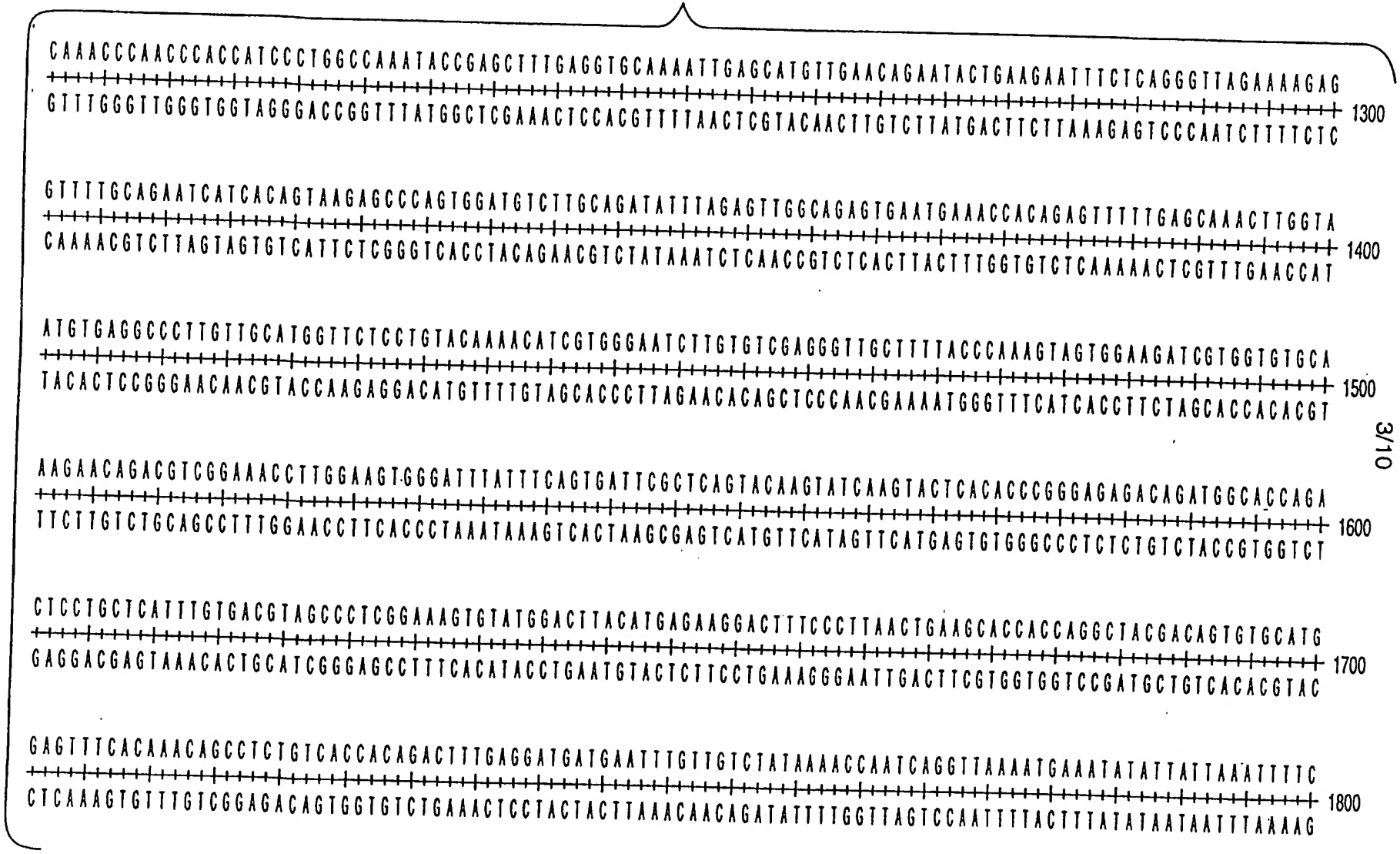

CAAACCCAACCCACCATCCCTGGCCAAATACCGAGCTTTGAGGTGCAAAATTGAGCATGTTGAACAGAATACTGAAGAATTTCTCAGGGTTAGAAAAGAG
GTTTGGGTTGGGTGGTAGGGACCGGTTTATGGCTCGAAACTCCACGTTTTAACTCGTACAACTTGTCTTATGACTTCTTAAAGAGTCCCAATCTTTTCTC
1300
GTTTTGCAGAATCATCACAGTAAGAGCCCAGTGGATGTCTTGCAGATATTTAGAGTTGGCAGAGTGAATGAAACCACAGAGTTTTTGAGCAAACTTGGTA
CAAAACGTCTTAGTAGTGTCATTCTCGGGTCACCTACAGAACGTCTATAAATCTCAACCGTCTCACTTACTTTGGTGTCTCAAAAACTCGTTTGAACCAT
1400
ATGTGAGGCCCTTGTTGCATGGTTCTCCTGTACAAAACATCGTGGGAATCTTGTGTCGAGGGTTGCTTTTACCCAAAGTAGTGGAAGATCGTGGTGTGCA
TACACTCCGGGAACAACGTACCAAGAGGACATGTTTTGTAGCACCCTTAGAACACAGCTCCCAACGAAAATGGGTTTCATCACCTTCTAGCACCACACGT
1500
AAGAACAGACGTCGGAAACCTTGGAAGTGGGATTTATTTCAGTGATTCGCTCAGTACAAGTATCAAGTACTCACACCCGGGAGAGACAGATGGCACCAGA
TTCTTGTCTGCAGCCTTTGGAACCTTCACCCTAAATAAAGTCACTAAGCGAGTCATGTTCATAGTTCATGAGTGTGGGCCCTCTCTGTCTACCGTGGTCT
1600
CTCCTGCTCATTTGTGACGTAGCCCTCGGAAAGTGTATGGACTTACATGAGAAGGACTTTCCCTTAACTGAAGCACCACCAGGCTACGACAGTGTGCATG
GAGGACGAGTAAACACTGCATCGGGAGCCTTTCACATACCTGAATGTACTCTTCCTGAAAGGGAATTGACTTCGTGGTGGTCCGATGCTGTCACACGTAC
1700
GAGTTTCACAAACAGCCTCTGTCACCACAGACTTTGAGGATGATGAATTTGTTGTCTATAAAACCAATCAGGTTAAAATGAAATATATTATTAAATTTTC
CTCAAAGTGTTTGTCGGAGACAGTGGTGTCTGAAACTCCTACTACTTAAACAACAGATATTTTGGTTAGTCCAATTTTACTTTATATAATAATTTAAAAG
1800

FIG. 1d

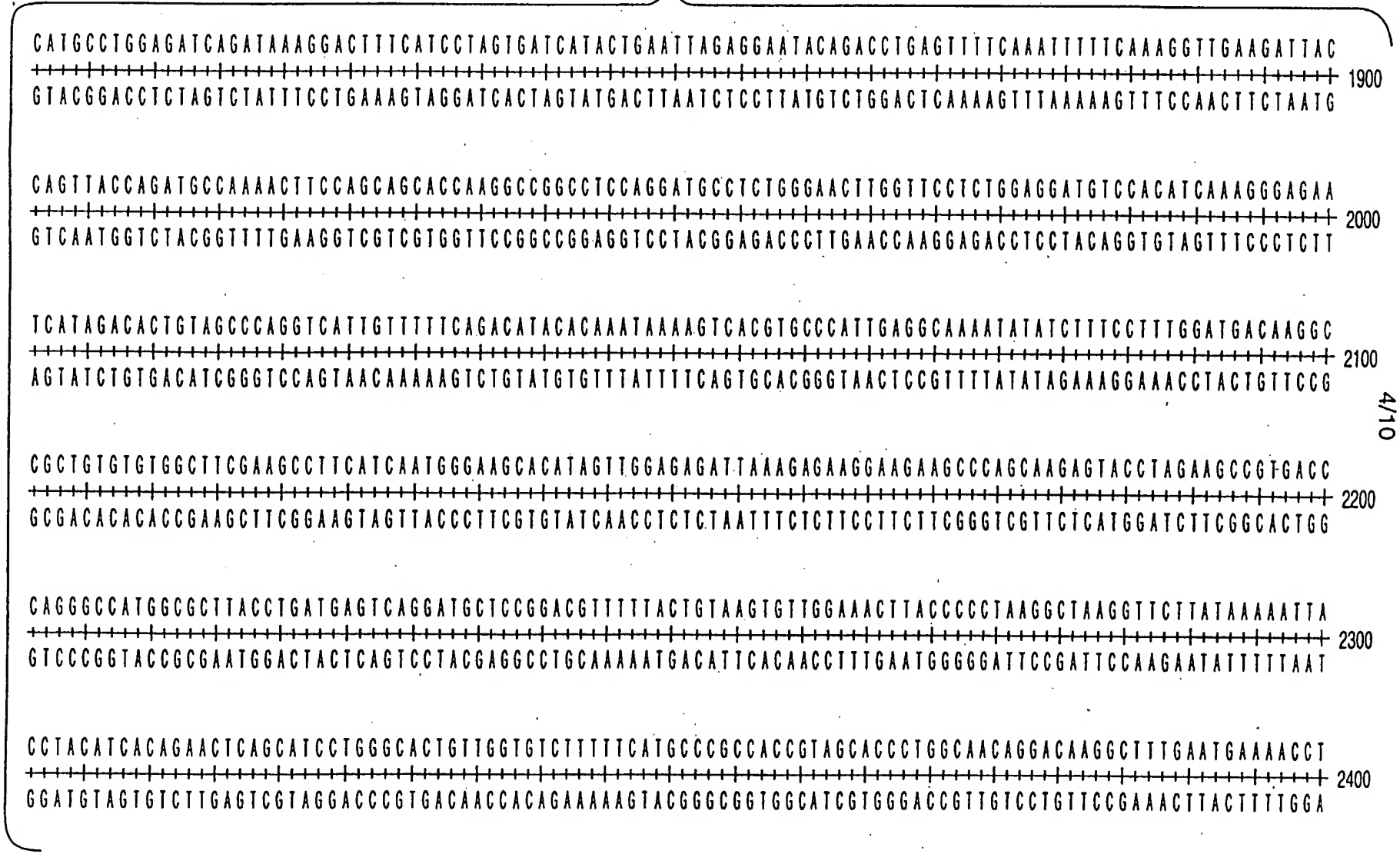


FIG. 1e

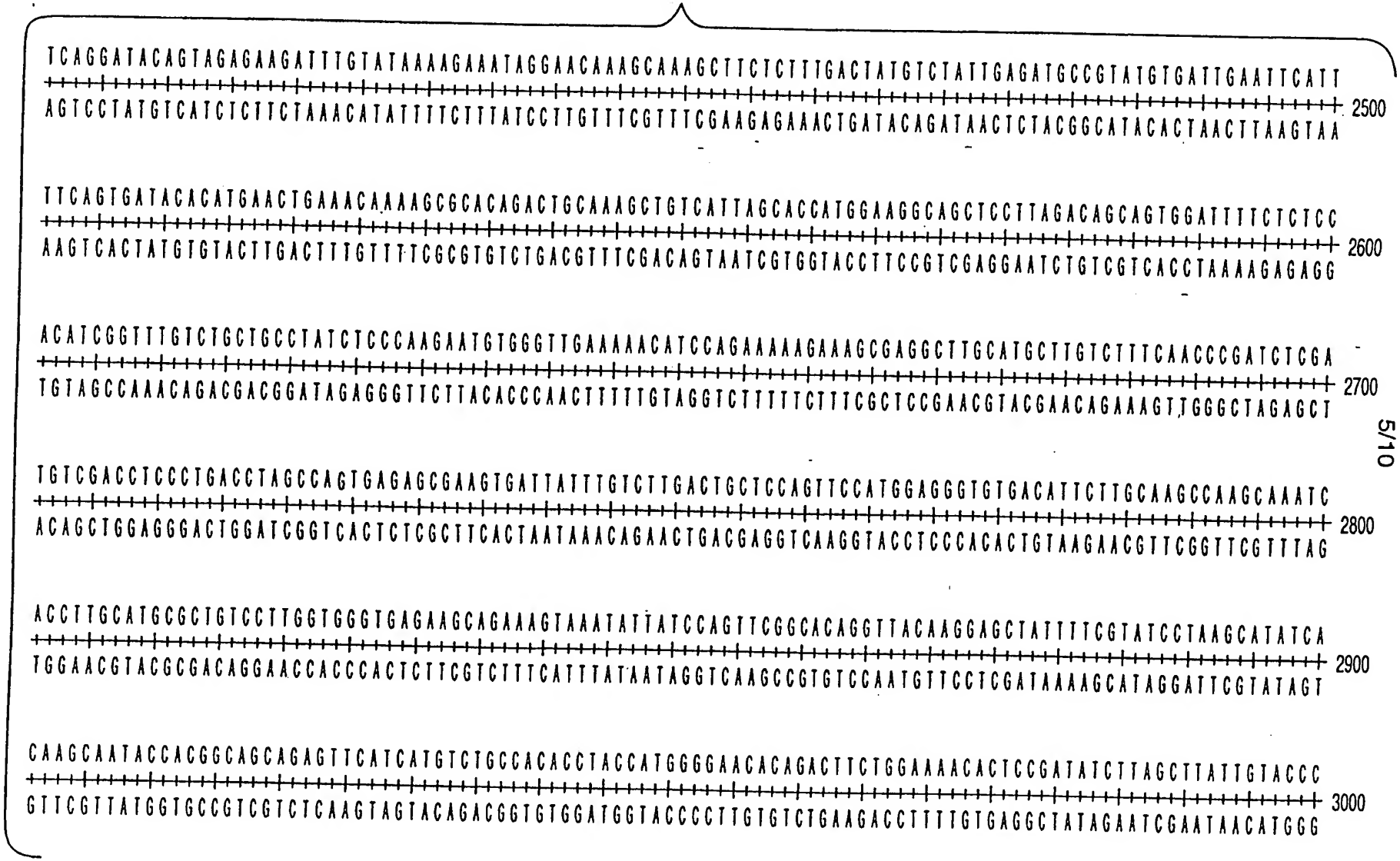
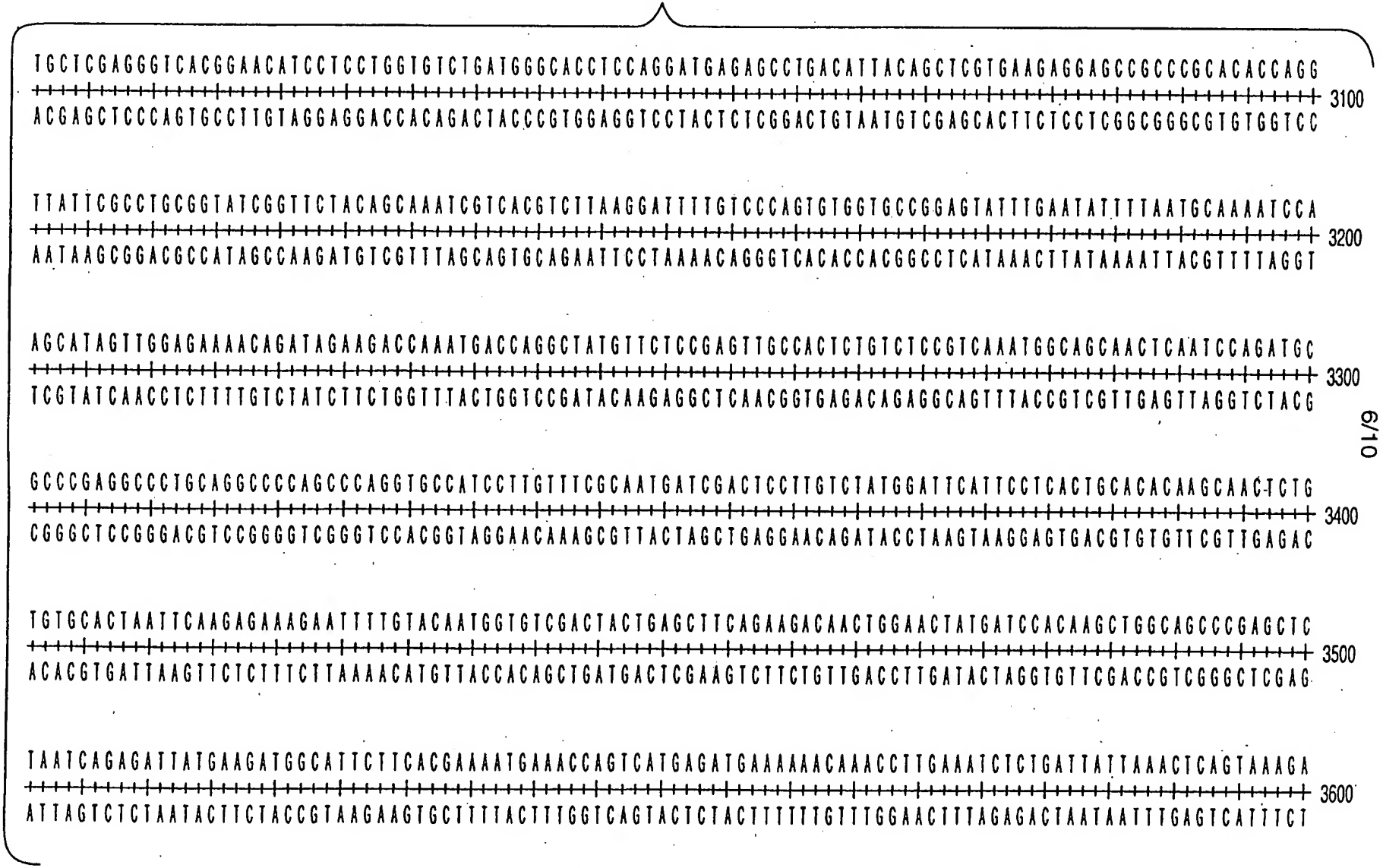
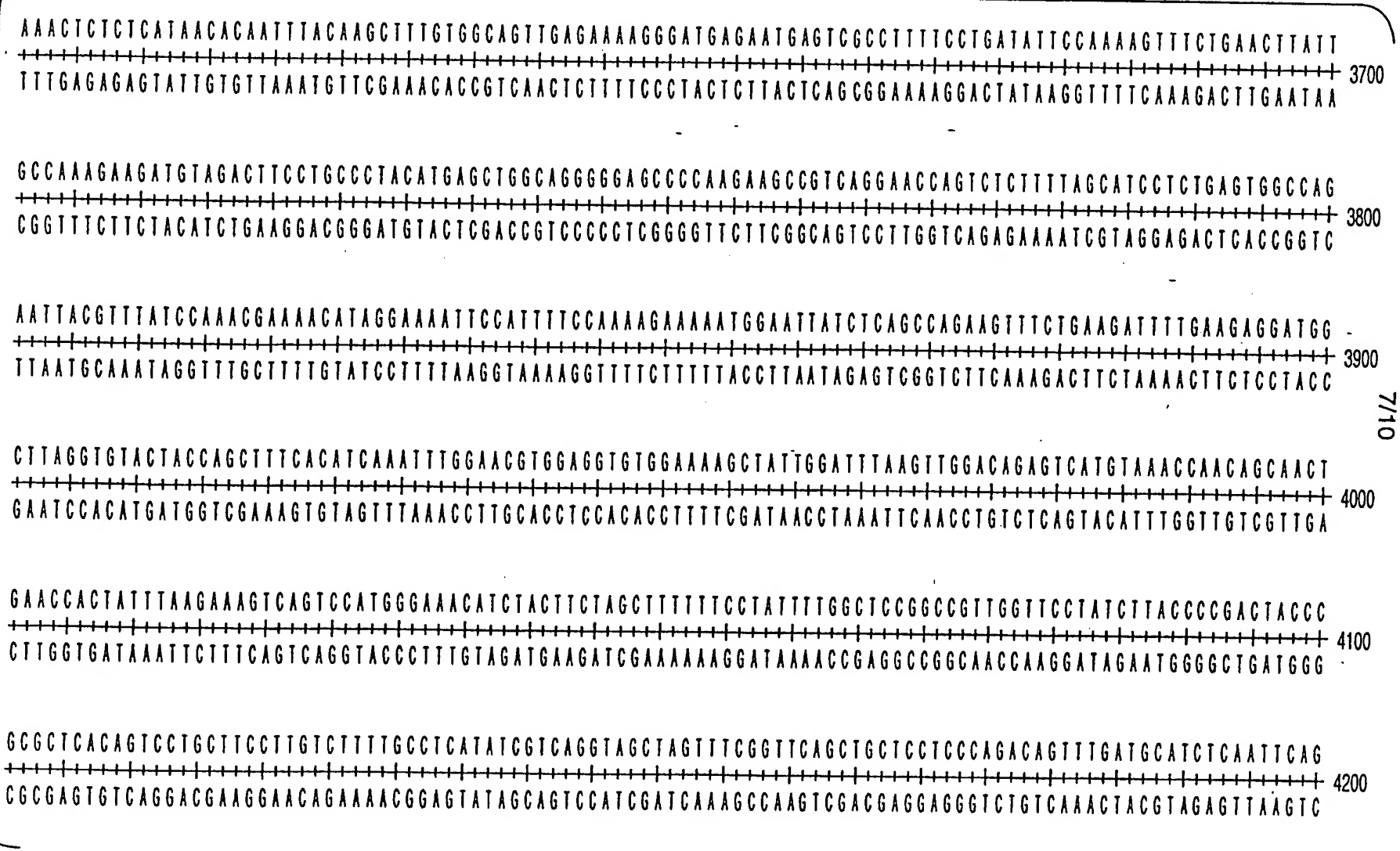

TCAGGATACAGTAGAGAAGATTTGTATAAAAGAAATAGGAACAAAGCAAAGCTTCTCTTTGACTATGTCTATTGAGATGCCGTATGTGATTGAATTCATT
AGTCCTATGTCATCTCTTCTAAACATATTTTCTTTATCCTTGTTTCGTTTCGAAGAGAAACTGATACAGATAACTCTACGGCATACACTAACTTAAGTAA
2500
TTCAGTGATACACATGAACTGAAACAAAAGCGCACAGACTGCAAAGCTGTCATTAGCACCATGGAAGGCAGCTCCTTAGACAGCAGTGGATTTTCTCTCC
AAGTCACTATGTGTACTTGACTTTGTTTTCGCGTGTCTGACGTTTCGACAGTAATCGTGGTACCTTCCGTCGAGGAATCTGTCGTCACCTAAAAGAGAGG
2600
ACATCGGTTTGTCTGCTGCCTATCTCCCAAGAATGTGGGTTGAAAAACATCCAGAAAAAGAAAGCGAGGCTTGCATGCTTGTCTTTCAACCCGATCTCGA
TGTAGCCAAACAGACGACGGATAGAGGGTTCTTACACCCAACTTTTTGTAGGTCTTTTTCTTTCGCTCCGAACGTACGAACAGAAAGTTGGGCTAGAGCT
2700
TGTCGACCTCCCTGACCTAGCCAGTGAGAGCGAAGTGATTATTTGTCTTGACTGCTCCAGTTCCATGGAGGGTGTGACATTCTTGCAAGCCAAGCAAATC
ACAGCTGGAGGGACTGGATCGGTCACTCTCGCTTCACTAATAAACAGAACTGACGAGGTCAAGGTACCTCCCACACTGTAAGAACGTTCGGTTCGTTTAG
2800
ACCTTGCATGCGCTGTCCTTGGTGGGTGAGAAGCAGAAAGTAAATATTATCCAGTTCGGCACAGGTTACAAGGAGCTATTTTCGTATCCTAAGCATATCA
TGGAACGTACGCGACAGGAACCACCCACTCTTCGTCTTTCATTTATAATAGGTCAAGCCGTGTCCAATGTTCCTCGATAAAAGCATAGGATTCGTATAGT
2900
CAAGCAATACCACGGCAGCAGAGTTCATCATGTCTGCCACACCTACCATGGGGAACACAGACTTCTGGAAAACACTCCGATATCTTAGCTTATTGTACCC
GTTCGTTATGGTGCCGTCGTCTCAAGTAGTACAGACGGTGTGGATGGTACCCCTTGTGTCTGAAGACCTTTTGTGAGGCTATAGAATCGAATAACATGGG
3000

FIG. 1f


TGCTCGAGGGTCACGGAACATCCTCCTGGTGTCTGATGGGCACCTCCAGGATGAGAGCCTGACATTACAGCTCGTGAAGAGGAGCCGCCCGCACACCAGG
ACGAGCTCCCAGTGCCTTGTAGGAGGACCACAGACTACCCGTGGAGGTCCTACTCTCGGACTGTAATGTCGAGCACTTCTCCTCGGCGGGCGTGTGGTCC 3100
TTATTCGCCTGCGGTATCGGTTCTACAGCAAATCGTCACGTCTTAAGGATTTTGTCCCAGTGTGGTGCCGGAGTATTTGAATATTTTAATGCAAAATCCA
AATAAGCGGACGCCATAGCCAAGATGTCGTTTAGCAGTGCAGAATTCCTAAAACAGGGTCACACCACGGCCTCATAAACTTATAAAATTACGTTTTAGGT 3200
AGCATAGTTGGAGAAAACAGATAGAAGACCAAATGACCAGGCTATGTTCTCCGAGTTGCCACTCTGTCTCCGTCAAATGGCAGCAACTCAATCCAGATGC
TCGTATCAACCTCTTTTGTCTATCTTCTGGTTTACTGGTCCGATACAAGAGGCTCAACGGTGAGACAGAGGCAGTTTACCGTCGTTGAGTTAGGTCTACG 3300
GCCCGAGGCCCTGCAGGCCCCAGCCCAGGTGCCATCCTTGTTTCGCAATGATCGACTCCTTGTCTATGGATTCATTCCTCACTGCACACAAGCAACTCTG
CGGGCTCCGGGACGTCCGGGGTCGGGTCCACGGTAGGAACAAAGCGTTACTAGCTGAGGAACAGATACCTAAGTAAGGAGTGACGTGTGTTCGTTGAGAC 3400
TGTGCACTAATTCAAGAGAAAGAATTTTGTACAATGGTGTCGACTACTGAGCTTCAGAAGACAACTGGAACTATGATCCACAAGCTGGCAGCCCGAGCTC
ACACGTGATTAAGTTCTCTTTCTTAAAACATGTTACCACAGCTGATGACTCGAAGTCTTCTGTTGACCTTGATACTAGGTGTTCGACCGTCGGGCTCGAG 3500
TAATCAGAGATTATGAAGATGGCATTCTTCACGAAAATGAAACCAGTCATGAGATGAAAAAACAAACCTTGAAATCTCTGATTATTAAACTCAGTAAAGA
ATTAGTCTCTAATACTTCTACCGTAAGAAGTGCTTTTACTTTGGTCAGTACTCTACTTTTTTGTTTGGAACTTTAGAGACTAATAATTTGAGTCATTTCT 3600

# FIG. 1g


AAACTCTCTCATAACACAATTTACAAGCTTTGTGGCAGTTGAGAAAAGGGATGAGAATGAGTCGCCTTTTCCTGATATTCCAAAAGTTTCTGAACTTATT
TTTGAGAGAGTATTGTGTTAAATGTTCGAAACACCGTCAACTCTTTTCCCTACTCTTACTCAGCGGAAAAGGACTATAAGGTTTTCAAAGACTTGAATAA 3700
GCCAAAGAAGATGTAGACTTCCTGCCCTACATGAGCTGGCAGGGGGAGCCCCAAGAAGCCGTCAGGAACCAGTCTCTTTTAGCATCCTCTGAGTGGCCAG
CGGTTTCTTCTACATCTGAAGGACGGGATGTACTCGACCGTCCCCCTCGGGGTTCTTCGGCAGTCCTTGGTCAGAGAAAATCGTAGGAGACTCACCGGTC 3800
AATTACGTTTATCCAAACGAAAACATAGGAAAATTCCATTTTCCAAAAGAAAAATGGAATTATCTCAGCCAGAAGTTTCTGAAGATTTTGAAGAGGATGG
TTAATGCAAATAGGTTTGCTTTTGTATCCTTTTAAGGTAAAAGGTTTTCTTTTTACCTTAATAGAGTCGGTCTTCAAAGACTTCTAAAACTTCTCCTACC 3900
CTTAGGTGTACTACCAGCTTTCACATCAAATTTGGAACGTGGAGGTGTGGAAAAGCTATTGGATTTAAGTTGGACAGAGTCATGTAAACCAACAGCAACT
GAATCCACATGATGGTCGAAAGTGTAGTTTAAACCTTGCACCTCCACACCTTTTCGATAACCTAAATTCAACCTGTCTCAGTACATTTGGTTGTCGTTGA 4000
GAACCACTATTTAAGAAAGTCAGTCCATGGGAAACATCTACTTCTAGCTTTTTTCCTATTTTGGCTCCGGCCGTTGGTTCCTATCTTACCCCGACTACCC
CTTGGTGATAAATTCTTTCAGTCAGGTACCCTTTGTAGATGAAGATCGAAAAAAGGATAAAACCGAGGCCGGCAACCAAGGATAGAATGGGGCTGATGGG 4100
GCGCTCACAGTCCTGCTTCCTTGTCTTTTGCCTCATATCGTCAGGTAGCTAGTTTCGGTTCAGCTGCTCCTCCCAGACAGTTTGATGCATCTCAATTCAG
CGCGAGTGTCAGGACGAAGGAACAGAAAACGGAGTATAGCAGTCCATCGATCAAAGCCAAGTCGACGAGGAGGGTCTGTCAAACTACGTAGAGTTAAGTC 4200

# FIG. 1h

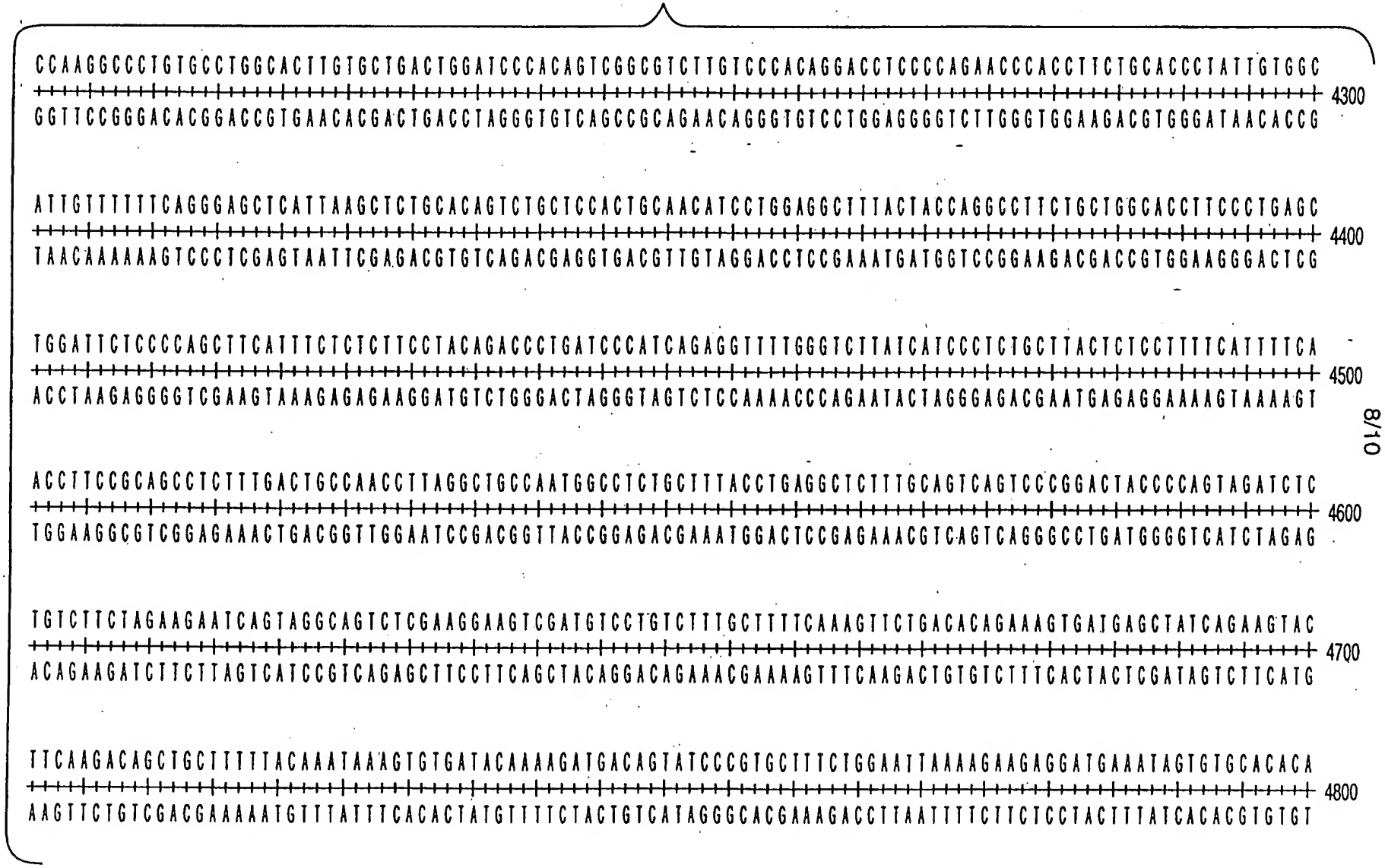

CCAAGGCCCTGTGCCTGGCACTTGTGCTGACTGGATCCCACAGTCGGCGTCTTGTCCCACAGGACCTCCCCAGAACCCACCTTCTGCACCCTATTGTGGC
4300
GGTTCCGGGACACGGACCGTGAACACGACTGACCTAGGGTGTCAGCCGCAGAACAGGGTGTCCTGGAGGGGTCTTGGGTGGAAGACGTGGGATAACACCG
ATTGTTTTTTCAGGGAGCTCATTAAGCTCTGCACAGTCTGCTCCACTGCAACATCCTGGAGGCTTTACTACCAGGCCTTCTGCTGGCACCTTCCCTGAGC
4400
TAACAAAAAAGTCCCTCGAGTAATTCGAGACGTGTCAGACGAGGTGACGTTGTAGGACCTCCGAAATGATGGTCCGGAAGACGACCGTGGAAGGGACTCG
TGGATTCTCCCCAGCTTCATTTCTCTCTTCCTACAGACCCTGATCCCATCAGAGGTTTTGGGTCTTATCATCCCTCTGCTTACTCTCCTTTTCATTTTCA
4500
ACCTAAGAGGGGTCGAAGTAAAGAGAGAAGGATGTCTGGGACTAGGGTAGTCTCCAAAACCCAGAATACTAGGGAGACGAATGAGAGGAAAAGTAAAAGT
ACCTTCCGCAGCCTCTTTGACTGCCAACCTTAGGCTGCCAATGGCCTCTGCTTTACCTGAGGCTCTTTGCAGTCAGTCCCGGACTACCCCAGTAGATCTC
4600
TGGAAGGCGTCGGAGAAACTGACGGTTGGAATCCGACGGTTACCGGAGACGAAATGGACTCCGAGAAACGTCAGTCAGGGCCTGATGGGGTCATCTAGAG
TGTCTTCTAGAAGAATCAGTAGGCAGTCTCGAAGGAAGTCGATGTCCTGTCTTTGCTTTTCAAAGTTCTGACACAGAAAGTGATGAGCTATCAGAAGTAC
4700
ACAGAAGATCTTCTTAGTCATCCGTCAGAGCTTCCTTCAGCTACAGGACAGAAACGAAAAGTTTCAAGACTGTGTCTTTCACTACTCGATAGTCTTCATG
TTCAAGACAGCTGCTTTTTACAAATAAAGTGTGATACAAAAGATGACAGTATCCCGTGCTTTCTGGAATTAAAAGAAGAGGATGAAATAGTGTGCACACA
4800
AAGTTCTGTCGACGAAAAATGTTTATTTCACACTATGTTTTCTACTGTCATAGGGCACGAAAGACCTTAATTTTCTTCTCCTACTTTATCACACGTGTGT

FIG. 1i

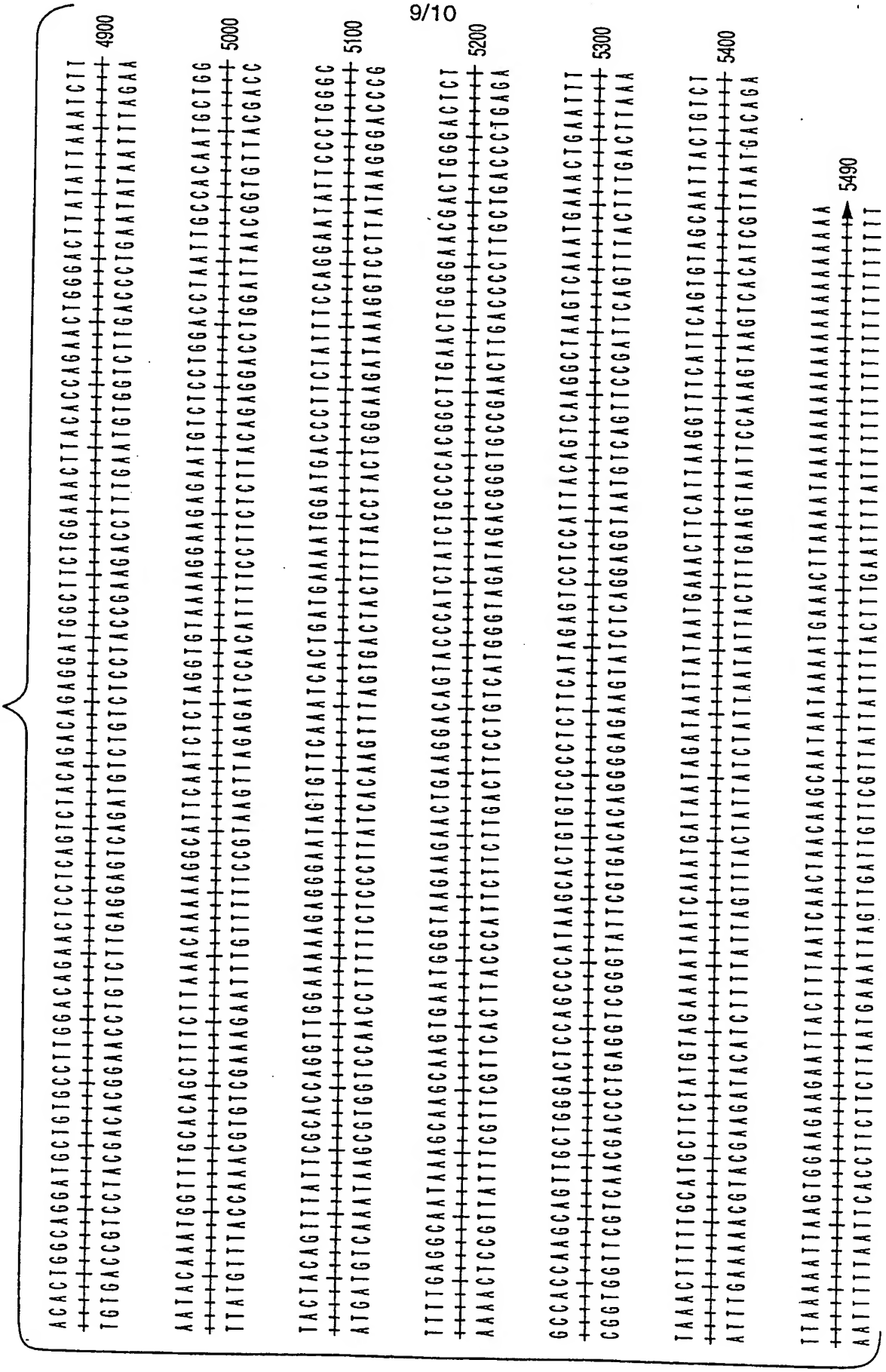
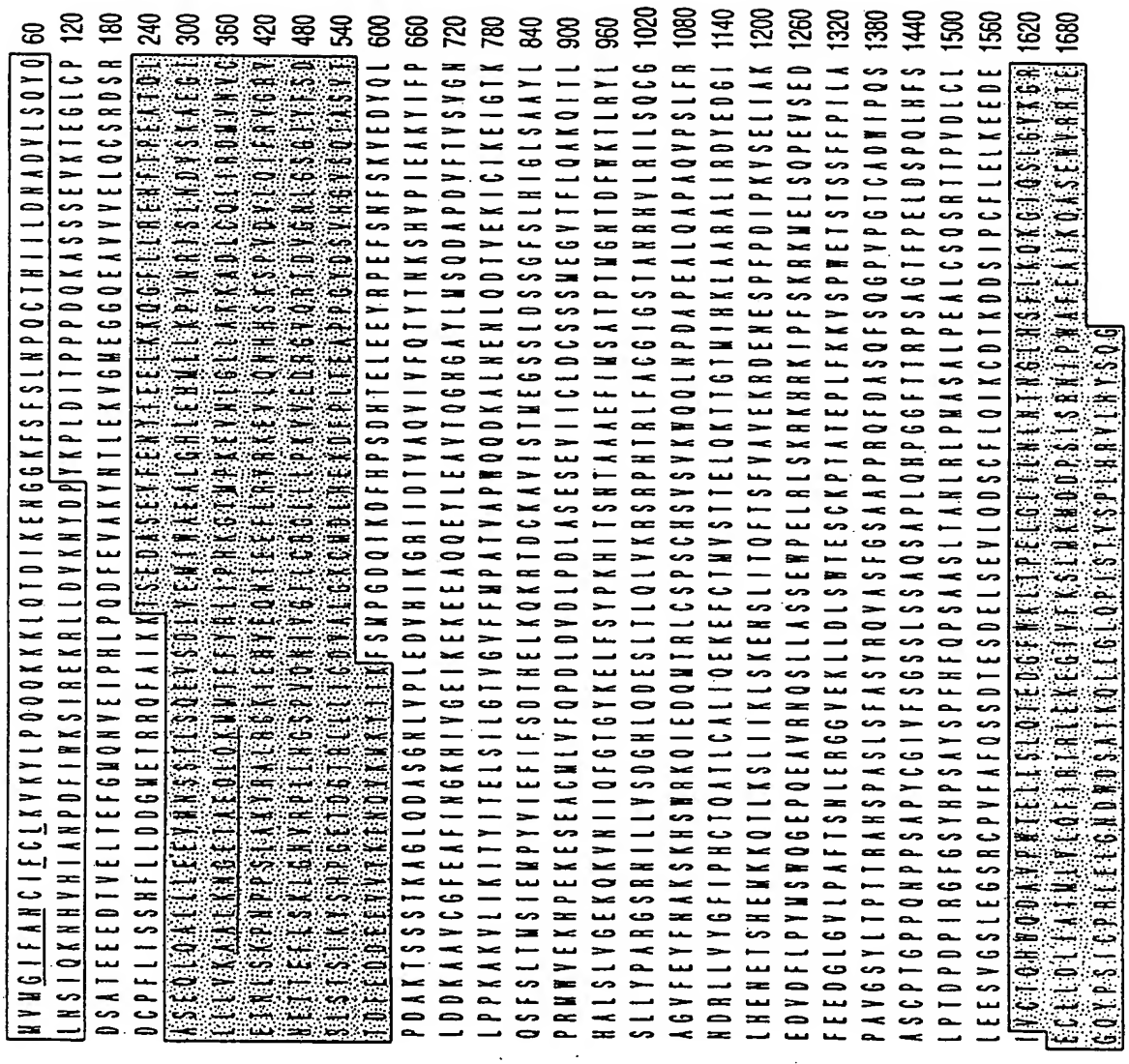


FIG. 2



# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/11348

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) :Please See Extra Sheet.
US CL :Please See Extra Sheet.
According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/130.1, 139.1; 435/6, 7.1, 70.21, 320.1, 325; 530/350; 536/23.1, 23.5, 24.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | KICKHOEFER, V. et al. Multidrug resistant cancer cell lines contain elevated levels of vaults. Proc. Amer. Assoc. Cancer Res., March 1997, page 252, abstract #1694, especially last 4 lines. | 1,2, 5-19 |
| X -- Y | SEBOLT-LEOPOLD, J. et al. Enhancement of Alkylating Agent Activity in vitro by PD 128763, a Potent Poly(ADP-ribose) Synthetase Inhibitor. Int. J. Radiation Oncology Biol. Phys., 1992, Vol. 22, pages 619-621, especially page 620, "Results" and Figures 1-3 and pages 620-621, "Discussion." | 36, 37 ------- 32, 33 |

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
| "B" | earlier document published on or after the international filing date | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" | document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "&" | document member of the same patent family |
| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
| "P" | document published prior to the international filing date but later than the priority date claimed | | |

| | |
|---|---|
| Date of the actual completion of the international search<br>15 SEPTEMBER 1999 | Date of mailing of the international search report<br>27 OCT 1999 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>PETER TUNG<br>Telephone No. (703) 308-0196 |

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/11348

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | KIM, K. et al. Tumor Suppressor Gene Expression during Normal and Pathologic Myocardial Growth. J. Biol. Chem., 09 September 1994, Vol. 269, No. 36, pages 22607-22613 | 1-37 |
| A | KICKHOEFER, V. et al. Vaults Are Up-regulated in Multidrug-resistant Cancer Cell Lines. J. Biol. Chem., 10 April 1998, Vol. 273, No. 15, pages 8971-8974. | 1-37 |
| X<br>-<br>Y | Database GenBank, Accession No. D79999, Nomura, N., Human mRNA for KIAA0177 gene, partial cds., DDBJ/EMBL/, see entire document. | 1-3, 5, 7, 11, 36<br>----------<br>20-23 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/11348

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

A61K 39/395; C12Q 1/68; G01N 33/53; C12P 21/04, C12N 15/63, 15/85, 15/11; C07H 21/04

A. CLASSIFICATION OF SUBJECT MATTER:
US CL :

424/130.1, 139.1; 435/6, 7.1, 70.21, 320.1, 325; 530/350; 536/23.1, 23.5, 24.5

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, MEDLINE, CANCERLIT, CAPLUS, DISSABS, BIOSIS, EMBASE, WPIDS, GENBANK
search terms: Leonard Rome, Valerie Kickhoefer, p193, p192, vault protein, lung resistance related protein, PD128763, 3-aminobenzamide